

The American Journal of DIGESTIVE DISEASES

The Official Publication of
THE AMERICAN GASTRO-ENTEROLOGICAL ASSOCIATION

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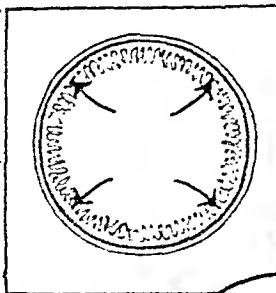
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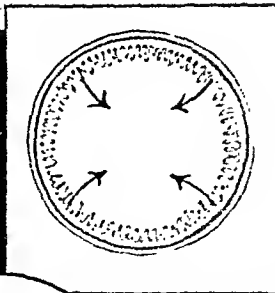
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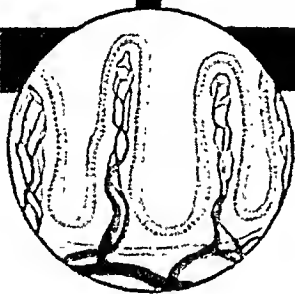
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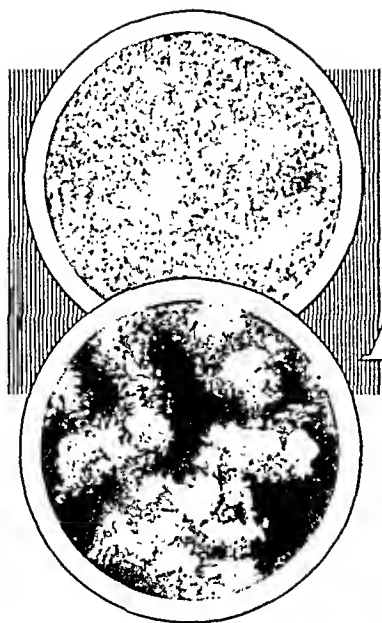
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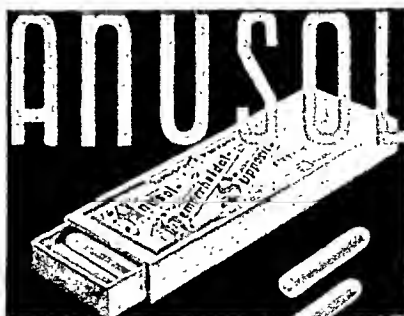
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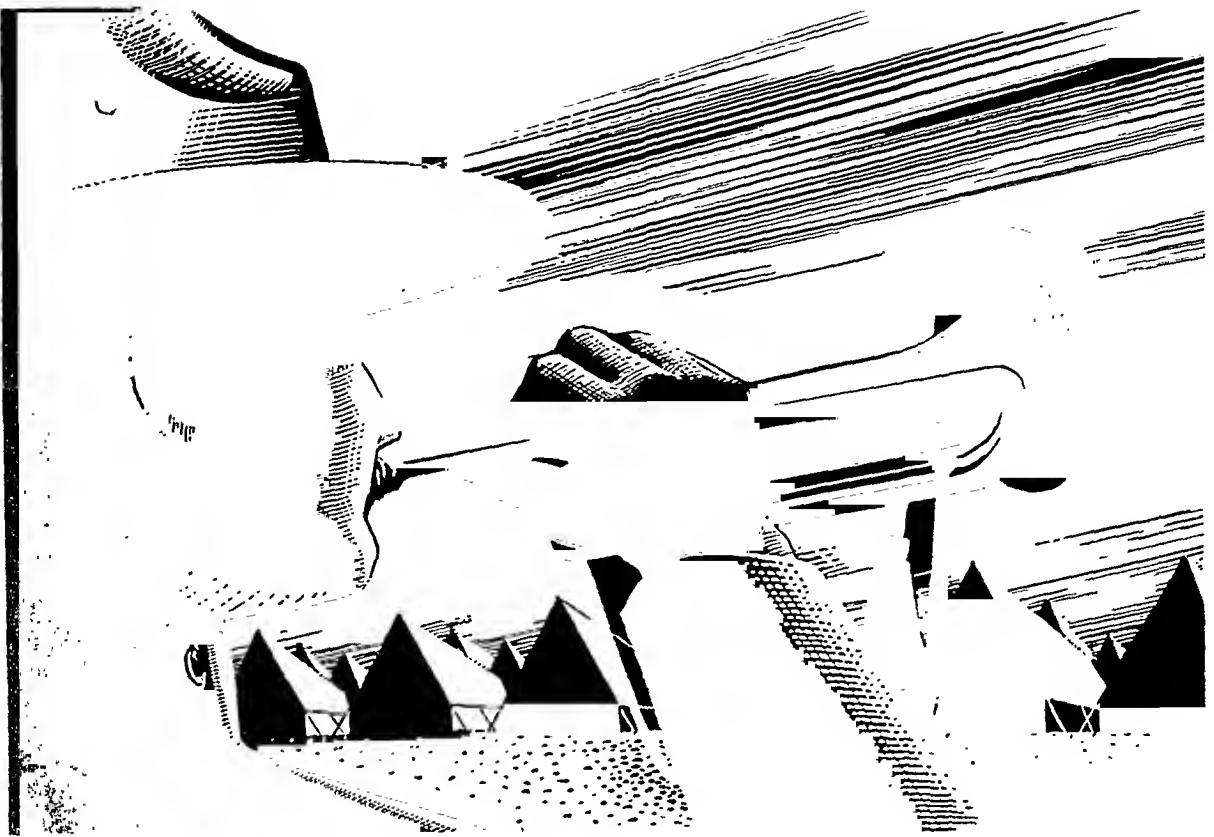
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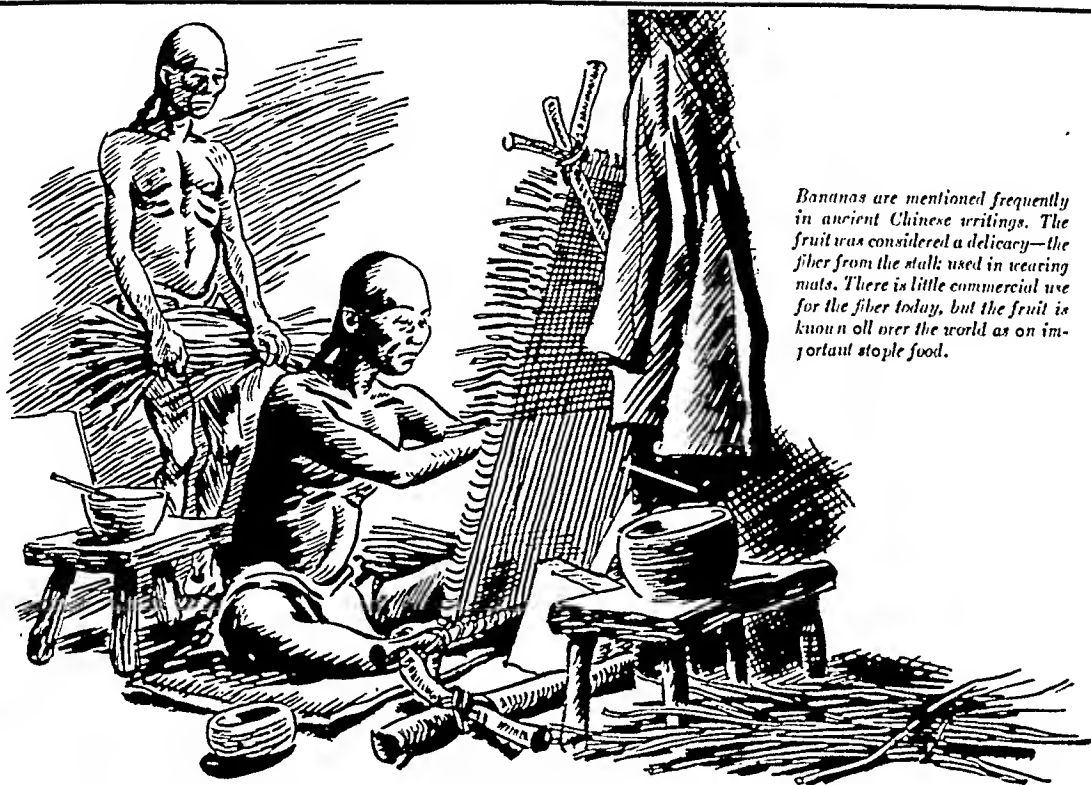


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Bananas are mentioned frequently in ancient Chinese writings. The fruit was considered a delicacy—the fiber from the stalk used in weaving mats. There is little commercial use for the fiber today, but the fruit is known all over the world as an important staple food.

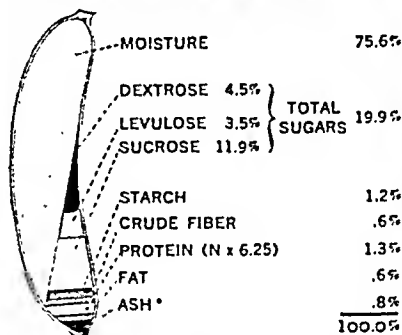
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IT is now recognized that the banana is a serviceable food under a wide range of conditions. As an energy food, which assists by virtue of its mineral and vitamin content in regulating body functions, it is useful in normal diets at all ages. In disease it is suited for some of those conditions in which the maintenance of proper nutrition is especially difficult. It is sometimes helpful under diametrically opposite circumstances—in both overweight and underweight, or in diarrhea and constipation.

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Caloric value (along with vitamins and minerals)....	Malnutrition
Satiety value and low fat (along with vitamins and minerals).....	Reducing Diets
Alkaline residue	Combating Acidosis
Vitamin content	Preventing Deficiency Diseases
Soft texture and blandness (with carbohydrates, vitamins, minerals, pectin and fiber).....	Intestinal Disturbances
	Normalizing Colonic Function
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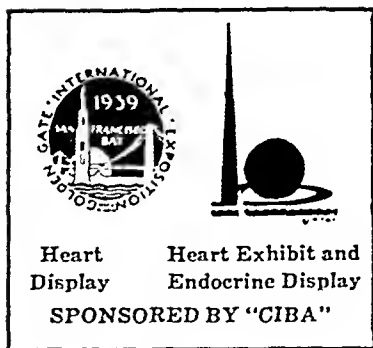
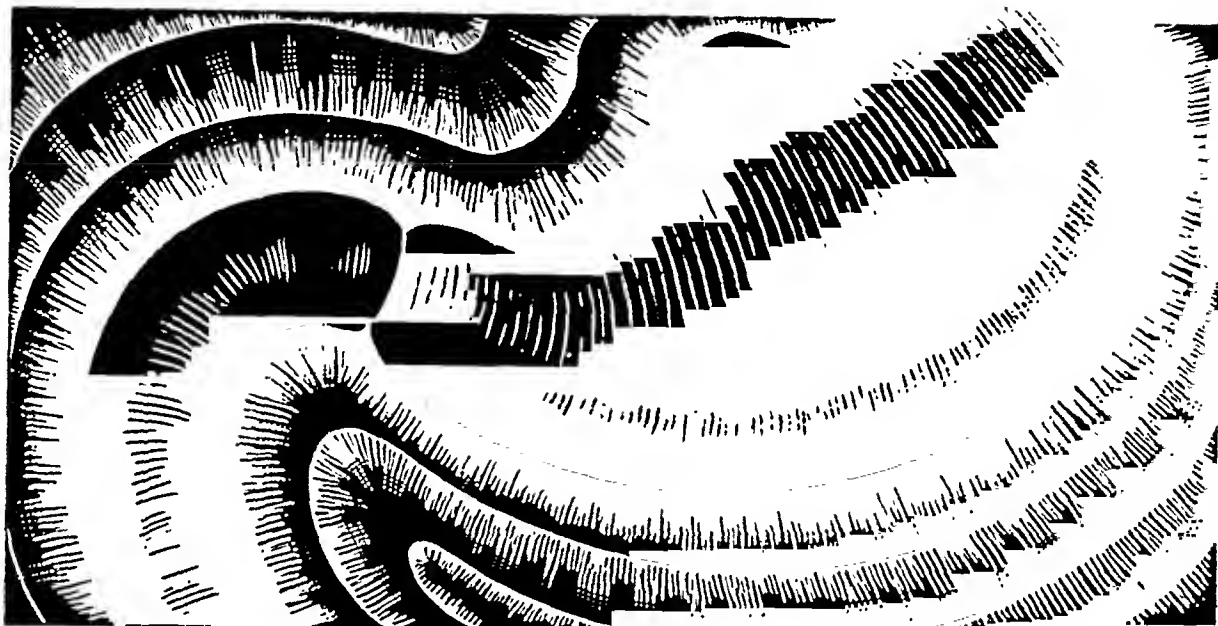
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(INDEX NUMBER)

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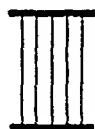
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The Diagnostic Value of Duodenal Drainage and Cholecystography in Gall Bladder Disease

Based on a Study of 137 Operatively Proved Cases

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THE importance of the recognition or elimination of gall bladder disease in every patient with digestive symptoms is indicated by the fact that in this clinic 30 per cent of such patients eventually are diagnosed as having cholecystitis with or without stone. The development of duodenal drainage and of cholecystography seemed at first to supply a final solution to the diagnostic problem, but, in spite of many encouraging reports on those procedures, clinicians generally still question their value. This, as we shall show, is justified in a strict sense for either test alone, but at the same time our observations on a small group of operatively proved cases indicate that the two procedures, taken together, rarely fail to be of diagnostic aid when the gall bladder is diseased: we are not at this time considering their diagnostic value in cases that have no gall bladder pathology.

In each of 137 cases one or more satisfactory duodenal drainages and one or more (often three or four) reliable cholecystographic investigations were secured before operation. When any question as to function by either test arose we were inclined to record it as good rather than as poor or impaired. When the gall bladders were removed, as 120 of them were, they were subjected to careful microscopic as well as

those with stone (100 cases) and those without stone but with evidence of some gall bladder pathology (37 cases). We shall discuss these groups separately, and, in addition, we shall refer incidentally to a third group, made up of cases from the first two, those having gall bladders of the "strawberry" type (12 cases).

AGE AND SEX INCIDENCE

The age and sex incidence resembles that of other authors and is shown in Table I.

HISTORY

The history was regarded as suggestive of gall bladder disease when the patient had had repeated but irregular attacks of right upper abdominal pain, with or without jaundice, or a long story of indigestion that was not obviously indicative of other abdominal pathology. It was positive in 87 per cent of the stone cases, 76 per cent of the no-stone cases and 75 per cent of the "strawberry" cases. In the remaining cases the diagnosis was made and operation advised solely on the basis of objective observations.

PHYSICAL EXAMINATION

The physical examination was looked upon as positive when it revealed tenderness, with or without a mass, under the right costal margin. It was positive in 61 per cent of the stone cases, 54 per cent of the no-stone cases and 66 per cent of the "strawberry" cases. The highest percentage in the "strawberry" cases is worthy of note.

CHOLECYSTOGRAPHY AND DRAINAGE

All of the cholecystographic examinations were made after the oral administration of tetraethylthalein, some of the patients being given the dye after dinner on the preceding evening only, others after both luncheon and dinner of the previous day. Films were made on an empty stomach early in the morning; two hours later, just before giving a fatty meal, and a half hour after the fatty meal. The independent opinion of our roentgenologist, E. P. Pendergrass, was accepted as to the concentrating ability of the gall bladder and as to the presence or absence of shadows indicative of stone.

Biliary drainage was performed in the early morning by the usual technique, except that both magnesium sulphate and olive oil were employed for stimulation of the gall bladder. We often found that when

TABLE I

The age and sex incidence of 137 operatively proved gall bladder cases

Age	Stone Cases		No-Stone Cases		Strawberry Type	
	Male	Female	Male	Female	Male	Female
20 - 30		10		3		1
30 - 40	5	26	1	9		2
40 - 50	3	55	5	10	1	3
50 - 60	6	13	3	4	2	3
60 - 70		1		2		
70 - 80	1					
	15	55	9	25	3	9

gross examination. The cases were unselected except that those having unsatisfactory preliminary study were eliminated. They fell into two main groups:

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the magnesium preparation was not effective a subsequent instillation of olive oil led to the evacuation of dark colored, concentrated bile.

In analyzing the data obtained by these two procedures it is necessary to distinguish clearly between the observations that have to do with gall bladder function and those that bear on the presence or absence of gall stones. In the roentgenological study, function was judged on the basis of the intensity of the gall bladder shadow; stones, on the presence or absence of negative shadows or on the presence of positive shadows without dye administration. In the drainage test, function was determined by the character of the bile obtained after stimulation (whether or not the so-called "B" fraction was obtained); stone, by the presence or absence in the drainage material of cholesterol or of cholesterol and calcium bilirubinate crystals.

Four diagnostic possibilities as to the condition of the gall bladder, on the basis of these tests, present themselves: (1) normal function and no stones, (2) impaired function and no stones, (3) normal function and stones, (4) impaired function and stones. Ideally one should be able, on the basis of either of the tests, to fit each case into one of these groups. That such a diagnostic classification is impractical in many instances, however, is indicated by the following discussion of our data.

Obviously when both roentgenological investigation and duodenal drainage show normal function and no evidence of stone one is inclined to eliminate gall bladder disease. As we shall show, however, operation may in such cases disclose some cholecystopathy: in these the diagnosis, if made preoperatively, rests chiefly on the basis of the history and the physical signs.

Impaired function as indicated by the two methods of study may be compared. Reference to Table 2 and Chart 1 shows that cholecystographic investigation revealed impaired function in 60 per cent of our stone cases, in 38 per cent of the no-stone cases and in 58 per cent of the "strawberry" cases. These results resembled, but were not identical with, the observations on a lack of "B" bile by drainage, which occurred in 50 per cent of the stone cases, 46 per cent of the no-stone cases and 66 per cent of the "strawberry" cases. The discrepancies will be referred to later.

Whether or not stones are present with the impaired function can not always be determined preoperatively. Thus when the gall bladder function is markedly im-

paired or the cystic duct is blocked, one does not get, on roentgenological investigation, sufficient dye concentration in the gall bladder to show negative stone shadows (indicative of stones composed largely of

TABLE II
Diagnostic significance of various observations in total group of 137 cases

Observations	Stone cases (100) per cent	No-stone cases (37) per cent	Strawberry cases (12) per cent
History suggestive	87	76	75
Physical signs suggestive	61	54	66
Cholecystography: (a) stone shadows	42	13	17
(b) lack of function	60	38	58
(c) stone shadows or lack of function	89	51	66
Duodenal drainage: (a) cholesterol crystals	50	16	33
(b) lack of function	50	46	66
(c) cholesterol crystals or lack of function	90	59	91
Duodenal drainage or cholecystography suggestive of some disease process	100	62*	100

*Includes cases showing only calcium bilirubinate in the drainage material.

cholesterin) or, on drainage, material from the gall bladder in which to search for crystals. Since these conditions are frequently present one cannot expect, by either method, to make, in a large percentage of the calculus cases, a positive diagnosis of stone. Stone shadows by roentgenography, however, were found in 42 per cent of our stone cases and, to our surprise, in 13 per cent of the no-stone cases. The drainage results indicated stones (cholesterol crystals) in an even larger percentage of the stone cases (50 per cent), and in 16 per cent of those without stone. In most of those positive for stone by the roentgen ray and by drainage, therefore, function was not completely absent.

In estimating the total incidence of gall bladder disease, as indicated by these tests, it is necessary, therefore, to include all the cases that show either impaired

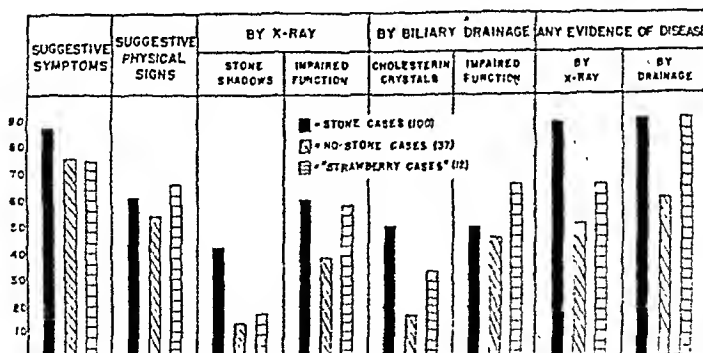


Chart 1. Percentage distribution of diagnostic observations on 137 cases of proved gall bladder disease (from Table II).

function or evidence of stone. Some show both; some, one or the other. On this basis 89 per cent of our stone cases showed gall bladder disease by roentgenography and 90 per cent by biliary drainage; of the no-stone cases, 51 per cent by cholecystography, 59 per cent by biliary drainage. The latter figure is increased if calcium bilirubinate alone is considered indicative of disease.

Kirklín (1) states that in his series of 415 operative proved cholelithiasis cases 99 per cent yielded positive cholecystographic data and that 70.8 per cent were diagnosed as having stones. He does not state specifically, however, that negative stone shadows were found in the 70.8 per cent; that hardly seems possible in view of the large number of our cases that showed no concentration of the dye in the gall bladder. Some of his cases, however, like some of ours, may have had positive shadows. Palmer's (2) data on a group of 131 stone cases are more consistent with our own: he found either stone shadows or non-visualization of the gall bladder in 94.7 per cent, and since 71 of his cases showed non-visualization it may be calculated that only 60 (46 per cent) showed stone shadows. On the other hand, Bockus, Shay, Willard and Pessel (3), in a series of 148 proved cases of cholelithiasis, found a positive stone diagnosis suggested by cholecystography in only 29.2 per cent, whereas it was suggested by drainage in 83.2 per cent; as suggestive of gall bladder dysfunction or disease, they found cholecystography helpful in 88.4 per cent, drainage in 98 per cent.

TABLE III

Conflicting observations by cholecystography, by duodenal drainage and at operation

	Observations by					
	Cholecystography		Duodenal Drainage		Observations at operation	
	Stone shadows	Function	Crystals*	Function	Stones	No stones
(a)	0	good	B in 4 C in 5	±	8	0
(b)	1	good	B in 1 C in 4	good	0	5
(c)	0	good	0	absent or impaired	1	4
(d)	± in 2 0 in 5	absent in 5 impaired in 1	0	good	5	2
(e)	0	good	0	good	0	3

*"B" represents calcium bilirubinate, "C", cholesterol.

Stones were found at operation in 8 of our cases that showed crystals in the drainage material but, on roentgen examination, good gall bladder concentration, prompt emptying after a fatty meal and no stone shadows (Table 3 (a)). In 3 of them, however, only calcium bilirubinate pigment was recovered; in 4, cholesterol crystals alone, and in 1, both cholesterol and calcium bilirubinate crystals. The physical examination was positive in six of the eight cases. The history indicated the diagnosis in every instance. In this group absent stone shadows by the roentgen ray could have been due to such an increase in the density of the gall bladder shadow as to obscure the stones or

to so much calcium in the stones that they could not cast negative shadows: these observations indicate, as Rafsky (4) has claimed, that in some instances, in which the gall bladder retains its concentrating power and no negative shadows can be visualized by the roentgen ray, microscopy of the duodenal contents alone may indicate the diagnosis.

On the other hand, it would be surprising if one did not in an occasional case find crystals, even cholesterol crystals, in a patient with gall bladder disease who had not as yet formed a stone. Such crystals must begin to be precipitated at some time before a cholesterol stone is actually formed. In one of our no-stone cases that had showed crystals we searched diligently over the wall of the gall bladder and finally found a few very minute crystalline masses that proved under the microscope to be cholesterol in nature. This point deserves emphasis because Shay and Riegel (5) have claimed that the discovery of cholesterol crystals in the drainage material is pathognomonic of stone. Cholesterol crystals were found in 4 of our no-stone cases and curiously in all of them the roentgenological examination also suggested stones (Table 3 (b)). Eight of the no-stone cases showed calcium bilirubinate crystals, while but one of these was diagnosed cholelithiasis by the roentgen ray. Bockus, Shay, Willard and Pessel (3), in 1931, and Shay and Riegel (5), in 1936, stated that the discovery of both cholesterol and calcium bilirubinate crystals in the drainage material is pathognomonic of cholelithiasis, yet of our 37 no-stone cases 2 showed both varieties of crystals.

In search of an explanation of the roentgen diagnosis of stone in our no-stone cases we resubmitted to our roentgenologist the films of our 5 no-stone cases in which a roentgen diagnosis of calculus had been made, without his knowledge at the time of the operative findings or of our reason for so-doing, and in all but one of them he then expressed doubt as to the presence of stones, stating that the shadows might be due to gas in the colon. In only one instance, therefore, was an unequivocal roentgenological diagnosis of stone made in our 37 no-stone cases. It seems probable that less experienced roentgenologists frequently make the error of misinterpreting questionable shadows, and for this reason particularly the original diagnosis in our five cases is here recorded. In the one case no explanation for the negative shadow could be assigned.

Four no-stone cases and one stone case were able to concentrate the dye satisfactorily and also showed no crystals in the drainage material, but did show a lack of "B" bile (Table 3 (e)). These would have been accepted as normal cases except for the impairment of function, indicated only by the drainage test, and the facts that in all of them the histories were positive and in four tenderness under the right costal margin was demonstrable; in one, a mass was palpable. Operation revealed pericholecystic adhesions in all four of them, two having gall bladders of the "strawberry" type. These observations clearly indicate the importance of a detailed history and a careful physical examination in all instances and the significance of a variation from normal in any single laboratory result.

Pathology of the gall bladder as indicated by cholecystography, in the presence of completely negative drainage observations, was found only 7 times (Table 3 (d)). In 5 of these the gall bladder was not visualized; in 1, the concentration was slight but nega-

tive stone shadows were demonstrated; in the final 1, positive stone shadows were observed. Stones were found at operation in 5 of these patients.

It is appreciated that a failure of visualization of the gall bladder does not necessarily indicate a functionless gall bladder or a blocked cystic duct; it may be due to faulty excretion of the dye by the liver or, as Lake (6) has shown, to premature emptying of the gall bladder as a result of some disturbance in the action of the sphincter of Oddi. In spite of this, unless the liver is obviously diseased, we have felt justified in accepting a failure of visualization, under controlled circumstances, as evidence of gall bladder disease or of cystic duct obstruction. This proved correct in all of the cases covered in this report.

Both tests were entirely negative in only 3 instances (Table 3 (e)). In each of these dense pericholecystic adhesions to neighboring organs was the outstanding lesion. The history and physical examination were significant in all of them. Gall bladder adhesions may be the only evidence of pathology found at operation and, as Crohn (7) has stated, they may give rise to symptoms suggesting stones.

The "strawberry" gall bladder group is small (12 cases) but it will be observed (Table 2) that the concentrating power, as determined by each test, was more often impaired in this than in the no-stone group, that cholesterol crystals were present in only 33 per cent of the cases and that stone shadows were described in 17 per cent (stones present in 8 per cent). Although cholesterol crystals have been described as occurring frequently in cases of cholesterosis it will be noted that their incidence in our series was small: it was no greater than the presence of calcium bilirubinate. The mottled granular character of the mucosa

in one of our cases probably could have caused the shadows which were erroneously interpreted as due to stones.

CONCLUSIONS

1. In the diagnosis of gall bladder disease the history and the physical signs are of great importance and may occasionally justify operative therapy even in the presence of negative roentgenological and biliary drainage tests.

2. A positive diagnosis of stone in the gall bladder can be made on the basis of negative shadows by cholecystography or of cholesterol crystals in biliary drainage material in not more than half of the cases.

3. By means of either of these tests a diagnosis of gall bladder disease can be made in approximately 90 per cent of the cases with stone and in 50 to 60 of the cases without stone; but a strict diagnostic classification on the basis of the presence or absence of stone is frequently impossible.

4. Both tests should be employed routinely in suspected chronic gall bladder disease as a check on the information obtained from the history and the physical examination. In some instances one and in some, the other test will give important diagnostic aid; together they failed to be of help in only three cases of this series.

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Glucose Tolerance in Anacidity

By

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UNTIL recent years, gastric anacidity was generally believed to indicate disease of clinical importance even though the patient at the moment presented no serious symptoms. Latterly, however, the tendency has arisen to regard achlorhydria as an interesting but scarcely serious medical curiosity. This view is supported largely by the studies of Bloomfield and Pollard (1). In the general summary of their recent monograph on gastric anacidity they conclude that the lack of acid is, as a rule, an involutional phenomenon of no special clinical significance.

Our own observations do not support such an opinion. With Alvarez (2) we, too, have been impres-

sioned with the fact that the parietal cells of the stomach secrete hydrogen ions in a concentration a million times greater than that in the blood. One cannot accept categorically that nature should have singled out the stomach to produce a purposeless acid secretion. And then further to choose the mineral acid which ionizes most completely. Aside from any philosophical consideration of these facts, there is considerable evidence to show that the hydrochloric acid is concerned in many physiological processes other than its action in the stomach (3). The assumption is that these rôles for the hydrochloric acid find adequate compensation in anacidity, if no damage is to result. We believe from our studies that such compensation is often inadequate in the anacid patient.

A large literature on the effect of histamine upon

From the Samuel S. Fels Research Fund and the Gastro-Intestinal Division of Medical Service I, Mt. Sinai Hospital, Philadelphia, Pa. Read before the Section of Medicine, College of Physicians, March 22, 1937.

gastric secretion in relation to anacidity has accumulated, yet it has done nothing to explain the mechanism of anacidity, nor has it presented anything tangible to establish or deny its significance. Our own feeling is that the approach to the problem of anacidity has been much like the earlier approach to medicine generally.

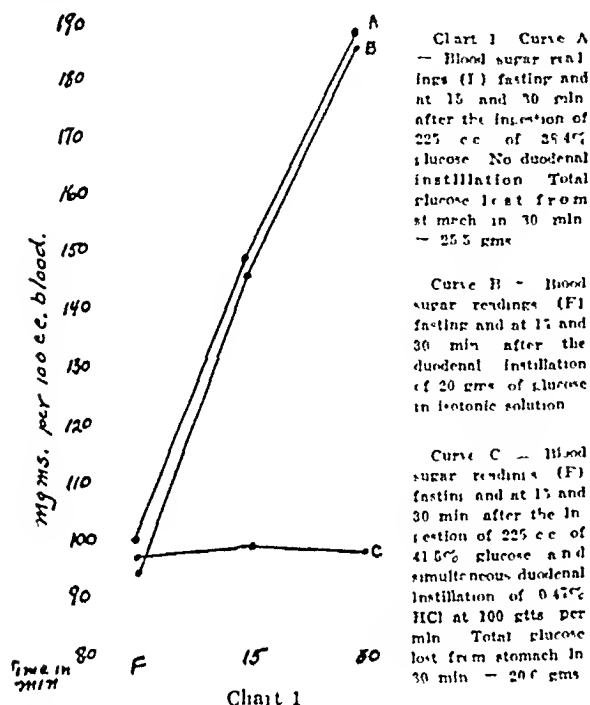


Chart 1

That is, it has represented essentially a pathological rather than a physiological approach. A search has been made for palpable disease such as carcinoma and pernicious anemia in relation to anacidity, rather than for the more subtle physiological changes. We have stated recently (3) that anacidity may represent a change which has insidious and far reaching effects upon the body economy. We suggest even that some of the changes which we now accept as natural involutional phenomena incident to advancing years may find a contributory factor in the increasing incidence of anacidity that accompanies these later decades. Vanzant, Alvarez, Dustermer, Dunn and Berkson (4), in their splendid studies on gastric secretion were of a similar mind because they observed a falling off in the frequency of anacidity after the sixth decade. They suggest that possibly "The persons with achlorhydria are not so hardy or long-lived as are those who have a strongly acid gastric juice."

By utilizing a method previously described (5) in studying the motor function of the stomach and pylorus, we (6) were able to show that there is present in the human duodenum a mechanism which when activated appears to stimulate the pancreas in the production of insulin, and helps in the prevention of alimentary hyperglycemia. In these studies we found that the absorption of amounts of glucose that would ordinarily produce very definite increases in the blood sugar concentration, failed to raise the blood sugar level when duodenal stimulation was applied simulta-

neously. In these studies as well as in our previous investigation of the motor function of the stomach and pylorus, we were led to believe that the gastric hydrochloric acid served as the intrinsic agent which supplied the duodenal stimulus.

Chart 1, illustrates the effect of the duodenal instillation of hydrochloric acid in the prevention of alimentary hyperglycemia. In a normal person, after an overnight fast, the stomach was intubated and venous blood was taken for blood sugar. Two hundred and twenty-five cc. of 38.4% glucose were then given by mouth. Venous blood was again collected at 15 and 30 minute intervals after the ingestion of the glucose. At the half hour interval the stomach contents were removed, the stomach lavaged with three 200 cc portions of water, and the total glucose remaining in the stomach was determined. It was found that 25.5 grams of glucose had left the stomach either by absorption, through the pylorus, or both. Curve A, shows the change in the blood sugar levels that resulted.

On another day the duodenum was intubated, fasting venous blood was collected and 20 grams of glucose in isotonic solution were instilled into the duodenum, and blood again taken at the 15 minute and 30 minute intervals. The result is shown in curve B.

Curve C shows the result following the ingestion of 225 cc. of 41.5% glucose and the simultaneous duodenal instillation of 0.47% HCl at the rate of 100 drops per minute. Special precautions were taken as described previously (6) to assure ourselves that none of the gastric contents left through the pylorus. We were thus able to show that at the end of 30 minutes 20.6 grams of glucose had been absorbed, yet in spite of such absorption no rise of the blood sugar occurred.

From our own experiments (6) we felt justified in assuming that the hydrochloric acid in the duodenum called forth an agent which helped in the prevention of alimentary hyperglycemia. Such an opinion is not

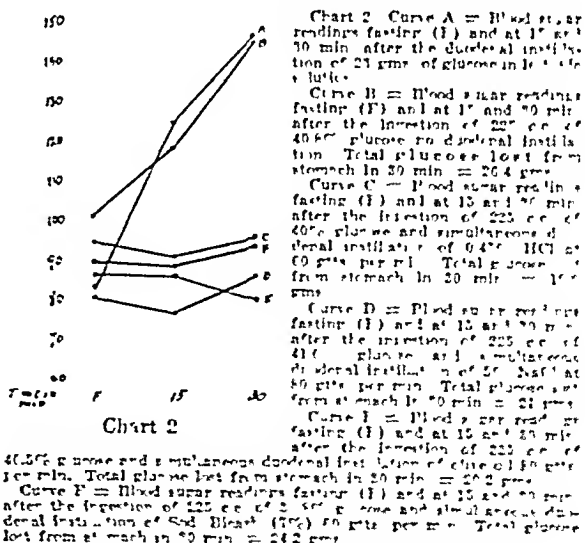


Chart 2

without support. Thus Freud and Saadi-Nazim (7) found a drop in blood sugar in dogs following the duodenal injection of 60 to 100 cc. of 0.5% hydrochloric acid. This was confirmed by La Barre and Ledrut (8), and Gley and Hazard (9) demonstrated that the duo-

Glucose Tolerance Curve in Fifty Anacid Patients

NO.	FAST.	30	60	120	180	REACTION
1	113.6	124.3	142.8	118.3	83.3	Neg.
2	90.5	133.1	151.5	87.7	76.8	Neg.
3	103.1	152.4	196.0	140.4	82.6	Plus 2
4	96.1	163.2	168.8	92.2	66.4	Neg.
5	69.0	117.0	148.2	79.2	74.1	Neg.
6	97.1	137.9	151.5	112.4	79.7	Neg.
7	117.6	162.6	190.5	172.4	78.1	Plus 2
8	83.7	143.4	149.2	144.9	110.5	Plus 2
9	96.6	145.4	201.0	131.6	73.5	Plus 2
10	118.3	168.0	196.1	176.2	118.3	Plus 2
11	98.5	156.2	153.8	97.1	89.9	Neg.
12	87.7	204.0	180.2	85.5	81.1	Plus 1
13	100.0	122.7	141.6	90.1	87.2	Neg.
14	88.9	151.5	195.4	134.2	103.4	Plus 2
15	68.7	108.7	170.9	222.2	138.4	Plus 3
16	97.1	157.5	190.9	144.9	103.1	Plus 2
17	87.3	250.0	229.8	170.9	128.4	Plus 3
18	97.1	138.9	119.7	90.7	85.1	Neg.
19	85.8	108.7	101.5	93.9	83.3	Neg.
20	84.0	129.8	132.4	81.6	97.6	Neg.
21	82.0	140.8	188.7	148.1	108.2	Plus 2
22	75.5	104.2	96.6	84.0	80.2	Neg.
23	84.0	117.0	188.6	129.8	102.7	Plus 2
24	86.9	146.1	187.9	138.9	107.2	Plus 2
25	93.4	129.8	168.0	166.7	126.2	Plus 3
26	96.1	139.9	111.7	100.5	111.1	Neg.
27	89.3	162.6	198.1	100.5	53.5	Plus 1
28	67.8	122.1	148.6	82.6	67.3	Neg.
29	77.8	139.9	135.1	113.0	110.0	Neg.
30	99.0	155.0	192.4	132.4	93.9	Plus 2
31	86.2	130.7	177.0	109.2	75.7	Neg.
32	79.4	132.7	110.5	93.0	100.2	Neg.
33	75.5	147.0	149.2	132.4	128.2	Plus 3
34	89.7	129.8	147.3	93.0	89.1	Neg.
35	90.9	143.9	138.0	94.5	89.3	Neg.
36	100.0	187.0	194.0	188.0	142.0	Plus 3
37	93.9	129.0	147.0	114.3	90.9	Neg.
38	80.0	125.8	87.3	79.0	71.4	Plus 2
39	98.6	168.0	177.0	186.9	152.7	Plus 3
40	97.3	113.6	133.3	103.1	94.6	Neg.
41	85.9	142.6	122.7	88.1	88.9	Neg.
42	83.3	163.3	180.2	144.9	60.3	Plus 2
43	94.0	129.8	132.8	97.6	81.6	Neg.
44	82.0	140.8	153.7	143.1	124.6	Plus 3
45	84.0	117.0	178.6	129.8	110.6	Plus 2
46	77.8	139.9	135.1	113.0	113.0	Neg.
47	99.0	155.0	172.4	132.4	93.9	Plus 2
48	90.9	143.3	136.0	98.5	88.3	Neg.
49	80.0	125.8	87.3	79.0	71.4	Neg.
50	74.6	177.0	190.5	161.3	143.9	Plus 3

TABLE I

denal injection of hydrochloric acid was followed in the circulating blood of the animal by a substance which could lower the blood sugar. Sugar reducing effects from hydrochloric acid were reported in human beings by Coelho and Oliveira (10), Boatini (11), and Conti (12). Elsewhere (6) we have shown that this mechanism in man operates largely through pancreatic islet stimulation. We wish to emphasize too, as we have done previously, that the duodenal effect is not called forth solely by hydrochloric acid, but that the gastric acid serves as the intrinsic activator of the mechanism.

Chart 2 illustrates the results when olive oil or hypertonic solutions of NaCl or Na HCO₃ were substituted for the HCl as the duodenal stimulant.

From these observations we were prompted to consider whether the anacid patient, in whom this intrinsic factor is lacking, would show a greater tendency to disturbed carbohydrate metabolism than would a similar control group of patients with normal or hyperacidity.

This report is based upon the study of the three hour glucose tolerance curve in fifty anacid patients and in a similar control group of patients with normal and hyperacidity. The objective studies on the anacid patients were done on an entirely unselected group. None of these patients clinically suggested any disturbance of carbohydrate metabolism. In all a routine blood sugar was within normal limits. None showed any evidence of neoplastic gastric changes. The test load consisted of 100 grams of glucose plus the juice of one lemon dissolved in water so that the total volume was 250 c.c. The test was done in the morning following an overnight fast. After taking venous blood for a fasting blood sugar, the glucose was administered and venous blood taken at 30, 60, 120 and 180 minutes thereafter. Blood sugar was determined by the Folin-Wu method.

In view of the increasing incidence of anacidity and abnormal glucose tolerance curves in the higher decades, selection of the control group was made from patients corresponding in age periods to those in the

Glucose Tolerance Curve in Control Group of Fifty
Normal and Hyperacid Patients.

NO.	FAST	30	60	100	180	REACTION
1	90.1	124.2	103.6	102.0	77.2	Neg.
2	93.5	129.0	112.4	92.7	80.1	Neg.
3	94.6	121.3	115.6	107.6	99.6	Neg.
4	73.4	126.0	123.9	94.6	91.7	Neg.
5	86.2	121.2	120.7	103.5	60.3	Neg.
6	99.6	183.5	234.0	84.4	66.7	Plus 1
7	95.9	151.1	100.0	97.7	77.5	Neg.
8	92.6	156.2	139.9	82.4	65.8	Neg.
9	94.4	159.7	109.3	102.5	70.4	Neg.
10	98.5	153.8	127.4	76.4	64.1	Neg.
11	79.7	123.7	126.6	74.9	72.1	Neg.
12	94.6	131.2	115.8	69.4	63.3	Neg.
13	99.0	184.2	164.3	99.4	92.1	Plus 1
14	75.2	146.0	179.2	111.1	82.1	Neg.
15	83.2	125.8	102.0	88.1	76.1	Neg.
16	94.6	107.5	120.5	109.1	81.2	Neg.
17	80.9	133.3	126.1	69.5	65.2	Neg.
18	83.9	145.6	204.0	106.7	132.1	Plus 3
19	88.4	136.1	106.4	93.9	78.1	Neg.
20	84.7	111.1	94.6	71.2	69.3	Neg.
21	73.0	150.2	95.1	74.6	72.2	Neg.
22	85.1	110.5	105.3	83.0	71.2	Neg.
23	82.0	151.5	101.5	111.1	75.7	Neg.
24	92.6	163.9	103.1	95.2	66.6	Neg.
25	88.5	91.7	122.5	92.9	83.0	Neg.
26	99.0	144.2	148.0	147.0	79.4	Plus 2
27	63.7	136.5	138.9	86.1	82.2	Neg.
28	63.7	129.0	132.4	105.9	97.6	Neg.
29	82.6	158.7	155.0	117.0	107.5	Neg.
30	94.4	129.8	121.2	113.0	82.3	Neg.
31	89.7	114.3	136.0	119.0	112.4	Neg.
32	103.0	165.3	202.0	134.2	86.9	Plus 2
33	99.6	128.2	111.0	101.1	107.5	Neg.
34	86.9	129.6	115.6	110.5	86.1	Neg.
35	81.7	165.9	113.0	97.6	92.2	Plus 1
36	80.5	144.8	107.5	91.3	75.2	Neg.
37	83.4	129.2	117.0	104.7	91.6	Neg.
38	92.2	140.0	133.3	119.7	111.1	Neg.
39	89.7	114.3	136.0	118.3	112.4	Neg.
40	91.3	126.6	129.9	82.0	72.4	Neg.
41	98.0	150.4	121.9	117.2	114.6	Neg.
42	77.1	187.5	154.2	92.6	98.9	Plus 1
43	86.2	164.0	127.9	111.2	73.4	Neg.
44	85.7	158.7	127.2	118.2	99.5	Neg.
45	82.4	122.6	122.2	109.1	92.4	Neg.
46	91.2	126.6	110.1	92.9	85.4	Neg.
47	79.6	127.6	120.1	112.2	91.4	Neg.
48	80.3	126.2	155.1	111.4	92.1	Neg.
49	42.2	124.1	122.1	108.0	73.9	Plus 1
50	67.2	124.2	122.2	111.6	72.4	Neg.

TABLE II

anacid group. The ages ranged from 29 years to 54 years, with approximately the same number of cases in each decade in both groups.

RESULTS AND DISCUSSION

Since there is no unanimity of opinion on the criteria that establish the normality of a glucose tolerance curve, we have classified our results so as to grade the response according to the changes which are considered abnormal. Thus we have recorded as negative those curves which start with a fasting blood sugar below 120 mgms. per 100 c.c., reach a peak after the 100 grams of glucose of less than 180 mgms., and return at 120 and 180 minutes to levels below 120 mgms. As plus 1, we have included curves which start with a normal fasting level, reach a peak above 180 mgms. per 100 c.c. of blood, and drop below 120 mgms. at 120 and 180 minutes. Under plus 2, we have placed results which reached a peak above 180 mgms., remained above 120 mgms. at 120 minutes but dropped below 120 mgms. at 180 minutes. Included also as plus 2 curves

were those which showed a two hour reading above 120 mgms., although the peak did not exceed 180 mgms. We did so, because we believe that a prolonged curve is indicative of a greater disturbance in carbohydrate utilization than is a high peaked curve. Finally, in the severest grade of plus 3 were included those curves which in addition to the abnormal peak, were still above 120 mgms. at 120 and 180 minutes (Table III). Tables I and II show the results obtained in the two groups of people. In Table I, the anacid group shows an unusually high incidence of abnormal glucose tolerance curves as compared to the control series of normal and hyperacid patients in Table II. Appreciating that at times glucose tolerance tests may yield abnormal figures which are not confirmed when the test is repeated, we did a second tolerance test a week later on all cases which yielded a positive result. Those which failed to yield a second positive result were not included in this series. In the anacid group abnormal curves of one degree or another were found in twenty-four of the patients, an incidence of 48%. Of these,

two fell into our classification of plus 1, fourteen as plus 2, and eight as plus 3. In the control group only eight showed curves that deviated from the perfectly normal response. Of these five belonged to plus 1 group, two, to plus 2, and one, to plus 3, (Table IV).

TABLE III

	Peak (mgm. per 100 c.c.)	120 min. (mgm. per 100 c.c.)	180 min. (mgm. per 100 c.c.)
Normal	<150	<120	<120
Plus 1	>150	<120	<120
Plus 2	>150 >150	>120 >120	>120 >120
Plus 3	>150	>120	>120

It is interesting to note the difference in grouping of the abnormal sugar curves in the acid and non-acid groups. We see in the anacid group not only a higher incidence of abnormal curves but a distinct tendency for a greater deviation from the normal.

Does the high incidence of abnormal tolerance curves in the anacid group represent a large percentage of mild and potential diabetics, or does it merely represent evidence of a disturbed duodenal mechanism because of the anacidity? Our own studies make us feel that anacidity is probably not infrequently a determining factor in the production of abnormal tolerance curves. Such an opinion is fortified by the changes in the glucose tolerance, in different age groups, noted by some observers. From the splendid studies of Vanzant, Alvarez, Eusterman, Dunn and Berkson (4), of Keefer and Bloomfield (13), of Dedichen (14), and of Davies and James (15), the relation of increasing age to a rising incidence of anacidity has been clearly shown. It is probably, then, more than coincidence that a diminishing sugar tolerance should be met with under similar circumstances. Thus John (16) found the glucose tolerance curve normal in 82% of children

but only 62% of adults. Similar results were reported by Spence (17). Hale-White and Payne (18) concluded that the sugar tolerance curve in old age showed a higher rise and a slower fall than the usually accepted standards and Marshall (19) obtained curves typical

TABLE IV

Abnormal glucose tolerance curves

	Acid Group	Anacid Group
Plus 1	5	2
Plus 2	2	14
Plus 3	1	5

of mild diabetes in 14% of healthy old persons, although none of them showed any symptoms of diabetes.

SUMMARY

Fifty anacid and fifty patients with normal and hyperacidity were studied with the three hour glucose tolerance test. After the ingestion of 100 grams of glucose, a surprisingly high incidence of abnormal curves was found in the anacid group. Forty-eight per cent of the anacid patients showed an abnormal glucose tolerance curve, while only 16 per cent of the control group showed such a disturbance.

The concern of normal duodenal activity with the presence of gastric hydrochloric acid and the relationship of that activity to the prevention of alimentary hyperglycemia are suggested as the mechanisms whose disturbance in anacidity may be responsible for the differences observed between the two groups. The higher incidence of abnormal glucose tolerance curves in advancing years is believed to be related to the higher incidence of anacidity in those age periods. It is our belief that anacidity represents not only a loss of gastric function but also is of real clinical significance in conditioning disturbed physiological states in parts of the body often quite remote from the stomach.

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Laxatives and Bowel Consciousness—A Clinical Study*

By

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THE unrestricted and indiscriminate sale and use of laxatives has resulted in purgative addiction by a large proportion of the American public. In order to obtain some facts in regard to the prevalent use of cathartics and the relation of constipation to the use of laxative drugs, a detailed laxative history was taken, along with the history of bowel habits in a series of 300 consecutive patients in private practice. Similar histories were taken on a number of patients at the gastro-intestinal clinics of the Newark Presbyterian and the Flower-Fifth Avenue hospitals. In view of the difficulty in obtaining accurate stories from clinic patients, the figures obtained from them are not reported. Their habits parallel those of the private group.

Nothing in this paper must be construed to refer to constipation due to organic obstruction (stricture or tumor), or constipation resulting from spinal cord disease.

Early in this study we ceased to regard constipation as a disease entity and dropped the differentiation between spastic, atonic, and rectal types as not worth considering either from the point of view of etiology or treatment. We have concluded that constipation as a disease entity does not exist; that constipation is a symptom arising in a person's mind. Every patient had a different conception of constipation. The use of laxatives is evidence of bowel consciousness, not of constipation.

This study represents a fair cross section of the public (Table I). 61 different diseases were represented. Of the 300 patients studied, 161 were males and 139 females. Table II shows the number in each age group. Only 2 patients declared that they had never taken a physic. Of the 300 cases, 36 females and 43 males took laxatives less frequently than 4 times a year (Table III). These 79 patients were excluded from the statistics regarding habit formation, for patients taking physics less often than once in 3 months can scarcely be considered bowel conscious. The incidence, therefore, of laxative addiction for the entire group was 73%. The proportion in males and females was exactly the same. This is in contradiction of the general opinion that more women take laxatives than men. Since laxative addiction and bowel consciousness go hand-in-hand, we can conclude that over 70% of our patients are sufficiently bowel conscious to take a laxative more frequently than once every 3 months. Further, in regard to the frequency of taking laxatives (Table III): of the 300 patients, 71 or 23% took laxatives daily. 161 patients or 53% of the whole group took laxatives weekly or more often.

We thought it of interest to determine how many

TABLE I

Chief Clinical Diagnosis	Cases
Irritable Colon	77
Gastro-Intestinal Neurosis	34
Duodenal Ulcer	23
Hypertensive Cardiac	25
Neurasthenia	18
Gastric Hyperacidity	16
Ulcerative Colitis	11
Rheumatic Cardiac	9
Cholecystitis	9
Acute Appendicitis	6
Arteriosclerotic Cardiac	7
Chronic Arthritis	7
Grippe	5
Cholelithiasis	5
Gastritis	5
Chronic Appendicitis	5
Syphilis	5
Achlorhydria	7
Diabetes Mellitus	3
Cathartite Habit	2
Hemorrhoids	1
Proctitis	5

2 Each:

Cancer of Rectum, Chronic Nephritis, Anemia, Duodenitis, Gastric Ulcer, Bronchial Asthma, Pulmonary T.B., Psoriasis, Male Depressive Psychosis.

1 Each:

Esophageal Cellulitis, Skin Cyst, Duodenal Diverticulum, Nephrolithiasis, Cancer of Esophagus, Incisional Hernia, Cancer of Stomach, Neurocirculatory Asthenia, Microscleritis, Tonsillitis, Erythema, Gynecomastia, Kidney, Hepatic Cirrhosis, Scleroderma, Strain of Abdominal Muscles, Cancer of Prostate, Pregnancy, Mesenteric Thrombosis, Cardiac Neurosis, Hyperthyroidism, Sympatheticotonia, Premature Ventricular Contractions, Cerebral Arteriosclerosis, Acute Gastro-Intestinal upset, Cancer of Vagina, Neuritis, Lymphatic Leukemia, Leber's Disease, Thyroid Cancer.

Total: 300.

different laxatives were taken regularly (Table IV). 95 or 43% of the group took only one type or brand of laxative. 72 or 32% took two brands of laxatives regularly, and two of the group took more than 8 different laxatives. A frequent reply to the question, "How many laxatives do you take?" is, "I take every thing I hear of."

While the common age of onset of the laxative habit for both males and females was between the ages of 20 and 30 (Table V), there is a greater disposition on the part of girls than of boys to form the habit under 20. This is probably due to the misconception that proper menstrual activity can persist only if associated with a daily copious bowel excretion.

As to the years of duration of the laxative habit (Table VI): 112 of the patients had been addicted for

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‡Since the writing of this article 474 additional cases have been interviewed with essentially the same findings.

less than five years, but 108 had been taking laxatives from 6 to over 40 years. There was no significant sex variation in the duration of the habit.

Table VII shows the various reasons given by patients for taking laxatives. The most frequent

traced the origin of their laxative habit to their parents. Mothers often insist that the children take a physic once a week, "to get a good cleaning out."

TABLE II

Age of Patient	Male	Female
0-10	2	1
11-20	8	8
21-30	25	33
31-40	46	36
41-50	40	21
51-60	17	23
61-70	18	14
71-80	5	5
Total	161	139

answer to the question, "Why do you take laxatives?" was, "my bowels can't move without one," and the next most frequent answer was, "When I get a pain in my stomach." Curiously enough 6 patients took laxatives for diarrhea and 9, merely because they thought, "they were good for you," and 2 on "general principles."

A study of the various laxatives taken (Table VIII) revealed that cleansing enemas were the most popular, with mineral oil a close second. Enemas were not popular with those who took laxatives frequently, and were rarely the only laxative taken. In enumerating the laxatives taken, the patient would usually conclude, "and occasionally, an enema." No differentiation was made between enemas and so called "high colonics." Those taking laxatives on a physician's order, usually took mineral oil or milk of magnesia.

The main purpose in studying these patients was to determine on whom to place the blame for the creation of bowel consciousness. Four groups are directly responsible: advertisers of laxatives, the medical profession, parents and friends. In the last group are included husband or wife. It is difficult to accurately determine how much the other three groups are influenced by advertising. We tried as best we could in each case to place the blame where it belonged. The advertisers (Table IX) were responsible as often as the other three groups combined. 21 of our patients

TABLE IV

Varieties of Laxatives Taken	Number of Patients
1	25
2	72
3	22
4	15
5	6
6	6
7	2
8	2
Over 8	2
Total	221

Several patients have told a similar story: "On Saturday night after our bath we were all lined up and given a tablespoonful of castor oil."

A second instance where parents can be blamed for starting the laxative curse is during puberty. At this time many girls look below par for reasons we cannot now go into. Mother asks, "Did your bowels move today?", and if the answer is "no" or "only a little," mother replies, "Oh my, you're going to have the same troubles I had. I had the same difficulty and had to take physics and have been forced to take them every other day for twenty years since." Mother then prescribes her favorite physic and daughter becomes bowel conscious and the laxative habit is started.

Many other examples might be quoted regarding the establishment of bowel consciousness and laxative habits by parents. In the presence of common colds, grippe, acute "stomach upset," or gastro-enteritis, the parents first impulse is to administer a purge. Not only is this "cleaning out" followed by constipation for which the child will often take another cathartic in a few days, but it also associates some malific influence in the child's mind between the fecal contents and these diseases. It is well known, that colds, grippe, and acute gastro-intestinal disturbances are self-limiting and that cathartics are of no particular benefit.

A contributing cause of America's bowel conscious-

TABLE III

Frequency of Taking Laxatives	Number of Patients	Less Than Once Every 3 Months
Daily	71	Males 43
Alternate Days	24	Females 36
Twice Weekly	23	Total 79
Weekly	43	
Twice Monthly	10	
Monthly	36	
Every 2 Months	14	
Total	221	

TABLE V

Age of Onset of Laxative Habit	Males	Females
0-10	5	12
11-20	5	22
21-30	45	85
31-40	26	15
41-50	19	10
51-60	9	6
61-70	7	2
71-80		1
	118	103

ness is the attitude of the medical profession. This attitude must be expressed from many angles. The physician not only frequently causes bowel consciousness on the part of the patient, but in the treatment of the average case of constipation he continues an

use of mineral oil or milk of magnesia post-operatively, and in many of our patients we have traced the onset of the laxative habit to this pernicious practice.

Physicians are markedly influenced toward the prescription of laxatives by the tremendous amount of

TABLE VI

Years Duration Laxative Habit	Males	Females	Total
0-5	70	43	113
6-10	21	17	38
11-15	9	13	22
16-20	11	16	27
21-25	3	3	6
26-30	1	3	4
31-35		1	1
36-40	1	3	4
Over 40	2	4	6
	116	103	221

already well established habit. I confess that I have rarely if ever witnessed any organic change result from the use of laxatives and many may ask, "Why bother about the subject if laxatives never hurt anybody." My answer is, that as physicians we must not only cure organic disease, but must help our patients over mental difficulties. The life of the average cathartic habitue is often made miserable and is as lacking in happiness as that of many sufferers from chronic organic disease.

How do physicians initiate bowel consciousness? How often on approaching the sick bed, we first ask, "Did his bowels move today?" Immediately, both patient and family are made bowel conscious. Post-operatively does not the surgeon put on his most sober expression and interrogate the nurse, "Have the bowels moved yet?" Many surgeons recommend the routine

TABLE VII

Patient's Reason for Taking Laxatives	Patients
Bowels can't move	74
Pain in stomach or distress	61
Gas	12
Get cleared out	11
Good for you	9
Distended abdomen	8
Headache	8
Hemorrhoids	6
Diarrhea	6
Rectal pain	4
Heartburn	3
Feel filled up	2

Nausea, General principles, Hard stools: 2 each.
Colic, Loss of pep, After dinner, Nervousness, Gall bladder attacks, Drooped colon, Don't feel well, Palpitation, Flushing: 1 each.
Total: 221.

TABLE VIII

Names Laxatives Taken	Patients
Enemata	70
Mineral Oil	61
Milk of Magnesia	33
Epsom Salts	27
Castor	24
Pills (name unknown)	22
Ex-Lax	16
Alophen	15
Castor Oil	15
Ararol	13
Magnesium Citrate	13
Freemint	8
Petrolagar	8
Car 14 and Bile Salts	6
Kondrenol	6
Sodium Phosphate	6
Pluto Water	6
Liver Pills	6
Senta	5
Sodium Sulphate	5
Herbs	5
Sal Hepatica	5
N.R.	1
Glycerine Suppositories	5

Seiditz Powders, Eco Fruit Salts, A. B. and E. Pills: 4 each.
Syrup of Figs: 3
Capsules (unknown type), Senzan, Sarska, Beal's, Oederlee, Regulin, Magnesium Oxide, Bile Salts, Lifebuoy Powder: 2 each.
Vernolate, Ecolax, Dr. Humphreys' Pills, Beechman's Pills, Calomel, Norol, Psyllium, Psyllium, Aloin Tea, Purgolax, Neo-Culic, Castorol, Mineral Water, Tarrax's Effervescent Salts, Italian Effervescent Salts, Lactolol, Doan's Laxative Pills: 1 each.

advertising which is directed at them. One month's accumulation of laxative advertising arriving by mail and clipped from Scientific Journals fills a legal sized folder. Try as he might the physician cannot escape the constant bombardment which draws his attention to "Habit Time," "Spastic Colitis," "The most prevalent ailment," and the superiority of "Miscibility," or "The physiological restoration of bowel rhythm."

In several instances in our series, in those cases listed as originating through the physician, we have obtained the following type story. "After my operation I had trouble with my bowels and until I left the hospital, I received an enema every day. When I arrived home my bowels did not move for two days, so I called the surgeon and he told me to take some magnesia. Later, when I went to his office he told me to take Petrolagar every night, and I have been taking it ever since." Unwittingly, the well meaning surgeon has started a pernicious habit.

The converse to what I stated previously is also true, while I have never known a cathartic to produce

serious organic change, I have never found the retention of feces for five or six days to result in any further hardship than a mild headache, a sense of fullness or a difficult passage.

The obstetricians are often the responsible party in the production of bowel consciousness. On the direc-

TABLE IX

Etiological Factors Stimulating Bowel Consciousness	Patients
1. Advertising	112
2. Physician	52
3. Parents	21
4. Friends	16
Total	221

tions issued to expectant mothers, the following statement often appears. "If the bowels do not move every day a mild laxative should be taken, either mineral oil, or milk of magnesia, or a low enema." How much better it would be to omit any mention of the bowels or to state, "If the bowels do not move for a day or two, do not become alarmed, they will eventually move of their own accord." It is routine on the part of many obstetricians to prescribe laxatives or enemas daily, post-partum. This practice had best be discontinued.

There is still another way in which we, as physicians, stimulate bowel consciousness and that is, in the treatment of constipation itself. Instead of belittling the patient's complaint, we take it seriously and prescribe measures to combat the "disease." This insistence on our parts to treat the condition, again is an instance of the provocation of the patient's imagination toward the association of retained feces and some dreadful scourge.

This paper does not touch on therapy, but as a

general rule the prescribing of cascara or bran or regulin or mineral oil preparations merely substitutes one laxative for another.

Lastly, we must touch on the influence of advertising on the establishment of bowel consciousness. 112 cases were traced directly to this source. The drug houses have taken advantage of the public's newly aroused health consciousness. Commercial success accrues to any manufacturer who can, by means of advertising create sufficient bowel consciousness in the public mind to sell a person only a few doses of his product. Since laxatives are usually habit forming, repeat orders pile up and a business is established.

Misbranding laxatives as candy and advertising to mothers to give regular doses of this or that purge assures not only one single sale, but continuous business even after the advertising stops. Some of our patients are taking "Liver Pills," and other proprietary preparations which have been advertised either to physicians or to the public for twenty or more years.

CONCLUSIONS

A program for the prevention of bowel consciousness on the part of the American public must be aimed at the source of this condition. First, parents must be educated against the use of laxatives and must be cautioned against over-emphasizing bowel function. Second, physicians must be more guarded in prescribing laxatives. They must show less concern regarding the functional activity of the colon. They must treat constipation by withdrawing laxatives and not by prescribing additional ones. Third, there must be a legal curb to the advertising of laxatives, in the press, and the radio, and by mail.

Imaginary diseases and symptoms are real to the patient. Patients' lives have been made miserable because of constant bowel consciousness and the constant use of laxatives. With 70% of our public addicted to laxation by drugs or enemas, it is high time that something be done about it.

The Treatment of the Individual in the Care of Peptic Ulcer^{*†}

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and

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ALTHOUGH it is generally recognized that there is no specific medical treatment for peptic ulcer, the alkali management with a dietetic regime as suggested by Sippy is accepted as a standard form of therapy. Internists and surgeons at present agree that there are definite complications of peptic ulcer which require surgical treatment but that in any case of peptic ulcer, a long period of carefully supervised medical treatment should precede any form of surgery. The surgeons are primarily interested in the various types

of operations, and the controversy has largely been as to the respective merits of gastro-enterostomy and gastric resection.

It is our purpose in this communication to emphasize the importance of the treatment of the individual as a whole. In addition to any accepted form of ulcer therapy, we feel it important to treat the individual as well as the ulcer. The treatment of the individual is not advocated as a specific method for the therapy of peptic ulcer, but follows the same principle as in other fields of medicine. However, it is our impression that such treatment has its greatest field in the domain of gastro-enterology.

Numerous observers have called attention to the

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importance of the personality in the etiology of ulcer. While we have recognized the importance of emotion, with tension and anxiety as factors in the etiology of ulcer, very little has been said regarding their role in the therapy. As a simple illustration of our thesis, it is known that a great many patients will be relieved of the symptoms of ulcer by a change of environment, by rest, or by simple modification of the diet, without medication. This relief or amelioration of symptoms has been interpreted either as a spontaneous abatement of symptoms, healing of the ulcer, or as something unexplainable. We suggest that combined medical and psychiatric study may explain such instances.

In approaching our problem it is essential first, to make a correct diagnosis of peptic ulcer. It is most important to differentiate between a functional syndrome of ulcer and a clinical picture due to an organic lesion in the stomach or duodenum. A good clinical history is the first essential in diagnosis. The experienced clinician readily appreciates the variability of the symptoms in the nervous dyspeptic and will easily exclude a functional disease. Ordinarily, in addition to the history we rely on direct X-ray evidence of ulcer, the presence of blood in the stomach contents and in the stools. In cases where all these laboratory findings are definite, the problem of diagnosis is not difficult. In the early cases of ulcer, the history may be typical but the X-ray examination may be indefinite and the laboratory evidence inconclusive. In such instances, the diagnosis depends on the evaluation of the individual; and every well-trained physician should be able to accomplish this. The psychiatrist has developed a technique of study of the individual which serves to elucidate functional factors. However, in the majority of instances, the general practitioner or the specialist may accomplish the same result because of his intimate knowledge of his patient, the patient's family environment and social background. There are, of course, some cases which definitely call for a more specialized psychological investigation, necessitating a psychiatrist.

In the course of history taking and of medical observation, a patient unfolds his problems to the extent to which the physician has established the confidence of the patient. The faculty of listening to the trials and tribulations of a business man or the disappointments of a love affair may not only serve to make a correct diagnosis, but tends to further therapeutics.

The general practitioner has often employed the verbal catharsis of the psychoanalyst without being aware that he was using a specialized technique, and this art has been lost by the specialist.

Internists and gastro-enterologists have always emphasized the greater importance of a history properly taken and evaluated, in the diagnosis of peptic ulcer, than any other clinical or laboratory test. We re-emphasize this point and add that in this history, the role of the individual as a whole be considered in relation to the symptomatology.

At the Mandel Clinic, Michael Reese Hospital, we have conducted our examinations of peptic ulcer patients in the form of a conference, the internist, the psychiatrist, the physiologist, the surgeon, and the social worker participating.

The social composition of our patients is much as in other clinics. All our patients are white, the propor-

tion of men to women is about twenty to one. Racially, sixty per cent of our patients are of Anglo-Saxon stock, and about forty per cent are Jews.

The routine procedure has been for the internist to take a careful history and make a complete examination. The history is supplemented by a complete report from the social service worker. An attempt is first made to make a clinical diagnosis on the basis of the history and the physical findings. In many instances the diagnosis is made before roentgen examination but in all cases, an X-ray is taken in the usual routine manner. The internist evaluates the clinical picture as a whole and then discusses the cases with the psychiatrist, the social worker, the physiologist, and the surgeon. Where the social problem is very prominent and can be treated by the Social Service Department, the physician will try to adjust his therapy to fit in with the social worker's program. When the emotional or psychogenic influences are the predominating factor, the psychiatrist will make a study of the patient and will make his recommendations, the patient remaining, however, under the observation of the internist.

Our experience with this approach has encouraged us a great deal. It becomes clear at once that a patient who is well adjusted socially has less concern about his symptoms than otherwise. The internist explains the nature of the ulcer symptoms to the patient. A simple routine of medical therapy for ulcer is instituted which consists of a soft diet, distributed in six feedings. Small doses of atropine may be added for a short period, and alkalies may or may not be administered. An explanation is given to the patient, also, of the importance of relaxation, the need of rest, vacations, and the relation of the emotional life to the symptomatology.

In studying the personality of the patient, one must begin with a thorough review of his major life reactions. It is a very good idea to get a general impression of the patient, especially in reference to his fundamental traits. Is the patient domineering, aggressive, restless individual, or is he an introverted, quiet, submissive, docile person? Has he been quite independent in his career as a member of society or has he always followed the lead of someone else? This is especially important as in quite a large number of our cases we found rather passive, submissive individuals, extremely dependent upon their mates, and yet revolting against them, as shown by a good deal of friction in their marital lives. In this connection, it is worth while to learn the sexual adjustment of such patients.

The industrial adjustment of such individuals is very interesting, especially from the point of view of their ability to hold a position during the medical treatment of ulcer and also following operation. This has been made the subject of a special study and will be reported later. (Meyer and Scher).

The patient's reaction to society and to his fellow-man is another important factor to which a good deal of attention must be paid. Very often the patient blames the difficult economic period, as well as his ulcer, as the cause of his industrial maladjustment. It is very difficult to determine whether the patient's maladjustment is due to his disease or to the particular economic stress to which he is being subjected. Clinicians have long recognized that a recurrence of symptoms can be associated with a severe emotional upset. In a great many instances it is possible to note

an amelioration of the symptomatology when the social-economic or sexual problem has been adjusted.

We wish to present now an outline of the various forms the therapist may employ depending on the nature of the case.

1. Hygienic Recducation.

With simple instructions in reference to rest, relaxation and divided food intake as suggested above.

REPORT OF A CASE

L. W., a young American, age 42, dress-salesman, bachelor, duodenal defect with deformity, duration 12 years, periodic recurrence despite treatment by various excellent clinicians. This patient had periodic recurrences each Spring and Fall, which were definitely associated with the tension of his business activities. With every season's change in style of dresses he was constantly returning to the same driving tension of a highly competitive and nerve-wracking business. His life was one constant rush from one city to another to obtain his orders, and it was then that his symptoms recurred. His bowel habits were bad and he constantly complained of constipation.

The first step in the patient's treatment was to explain the importance of a scheduled daily routine. The importance of relaxation in his business life and its relation to his symptomatology was made clear. A scheduled routine of diet was advised. Atropine, together with alkalis, was administered and the patient was asked to return for repeated observations. The patient was also asked to return especially at presensory periods—and also at periods of greatest emotional tension. This treatment gave very satisfactory clinical response. The symptoms abated, the retention diminished and the patient was able to continue at his occupation. He has had occasional recurrences, but these were mild in character. He is able to continue his work without interruption and sees the physician only when notified to do so.

2. Simple Suggestive Therapy.

When a patient is somewhat tense and anxious without any evidence of a clear-cut neurosis, simple suggestive therapy with medication is very much worthwhile and proves to be successful in a great many cases. One must remember that even atropine and alkalis have a very powerful suggestive effect, together with their specific value in ulcer therapy.

3. Therapy by Intellectual Insight.

In a good many cases the patient enjoys receiving a great deal of attention which naturally comes with any physical illness. This holds especially true in young, somewhat immature individuals with families who always have been over-protective, and in such cases there is a marked "secondary gain" from the illness. In these patients a review of the personality with explanation of some of the mechanisms of their behavior, results in gaining intellectual insight which helps them to change their attitude toward their illness and liberates them from a dependent position in the family.

4. Social Therapy.

As we have indicated, many of our cases may be caused by difficult social and environmental situations. In such cases proper environmental manipulation by the social worker, which gives the patient a sense of security in the unstable world which surrounds him, may lead to a marked improvement. In private

practice, where the agency of a social worker is not available, the physician must function in that capacity, as physicians always have functioned.

5. Therapy of a Dependent Attitude Upon Physician or Clinic.

There is a very important group of patients who are very faithful, and who come to the clinic time and again without showing any subjective improvement. Such patients become extremely dependent upon the clinic and especially upon the physician for whom they develop a deep emotional attachment. There is no question but that these patients have serious economic problems; but the more the physician tries to help them and understand them, the less improvement they show.

Case 2. A man of 46 has been coming to the clinic for a year and a half, complaining of epigastric distress recurring regularly after meals, associated at times with nausea and belching, relieved by intake of food and soda. Vomiting was present on occasions and severe night pain was particularly striking. Duration of symptomatology was approximately nine years. Both the patient and his wife were extremely proud people and it was only under considerable pressure that they consented to accept a certain amount of help. The patient was extremely touched by the physician's interest in him. On each consecutive visit he became more and more sentimental, shed copious tears, bemoaned his ill fortune and persisted in his gastro-intestinal complaints. An X-ray of the gastro-intestinal tract showed a duodenal deformity. Various types of medication were tried, without much relief. A study of the patient's background revealed the fact that the patient came from a stock where there was a great deal of admiration for religious learning. When the patient was a young man he became acquainted with the daughter of a distinguished clergyman who at that time came on a missionary tour to America. The patient was fascinated with the young woman and felt very happy when she consented to marry him. He became very ambitious and energetic and to prove his own worth he amassed a fair fortune. All this was lost in the depression, which was followed by a complete rejection of the patient by his wife. Hence, the extreme attachment to the physician, who in a sense, symbolized to the patient the same thing. The more the patient was helped, the more he wanted help and the less he improved. For this reason, a very drastic attitude was taken, with a complete change of attitude toward the patient. He was told that he must cease being a child, that he must go out and work, and face his responsibilities like a mature man. This was followed by a marked emotional display on the part of the patient and a rather quick adaptation to reality situations with marked diminution in symptomatology. Such radical treatment may be indicated in these types of cases.

6. Psychoanalysis: Patients with definite neurosis which can be helped only by intensive psychotherapy of a rather specialized kind, including psychoanalysis.

It is known that an ulcer may be symptomless. The general explanation has been that such ulcers occur in regions which may be termed "silent areas." Such ulcers may show symptoms only at the time of hemorrhage or perforation. Apart from the location of "silent areas," the absence of symptoms has been explained by the fact that their threshold for pain sensitivity is high. This probably is true, but it occurs to us that there are other factors which may serve to explain the absence of subjective symptoms. There are a number of ulcer patients who occasionally complain of distress, but it is either minimized by them or

does not register in their consciousness. When such patients become disturbed emotionally, or beset with special problems which they cannot meet, the symptoms of ulcer come to the foreground and it is then that they complain of their distress, and become aware of being ill. Hence the appearance of symptoms in emotional stress and conversely, the disappearance of symptoms when there is a favorable change in the total situation. This explains why simple removal from a difficult situation at home may help the patient without any medicinal therapy.

We doubt very much whether one can hope for a complete relief of symptoms of peptic ulcer in a maladjusted individual. In our experience, we have seen time and again, how even with the removal of pathology, patients remain ill and keep on returning to the Gastro-Intestinal Clinic, presenting new symptoms which are nothing but somatic conversions of their underlying emotional problems. This is also true of a patient with a healed duodenal ulcer and a social maladjustment.

The tendency of a peptic ulcer to heal spontaneously is well known. This is particularly true of gastric ulcer; and post-mortem studies reveal many healed ulcer scars. Duodenal ulcers likewise have a normal tendency to heal, irrespective of any form of therapy.

On the other hand, the treatment of ulcer by alkalies or any other form of medical management has its percentage of failure as well as its percentage of cure. Some of these failures may be definitely attributed to the complications of peptic ulcer, such as pyloric stenosis, penetration into the pancreas, perforation and hemorrhage, which require surgical intervention. There are, however, a percentage of failures following medical ulcer therapy of any type which we are unable to explain. The inability to explain or correct these failures has often resulted in needless operations, or patients have become cultists or confirmed neurotics. If we analyze these failures in the light of what we know of the individual, we may explain the origin of the symptoms and either with or without medicinal therapy obtain a favorable result. Thus our percentage of failures by medical therapy should be decreased.

Patients do have recurrences of symptoms, even if they are well-adjusted emotionally, and these recurrences may be due to activity in the ulcer itself. It is

equally true that patients have recurrent symptoms despite treatment by any accepted forms of ulcer therapy and these recurrences may also be associated due to activity in the ulcer. The reasons for the recurrences are apparently not always clear to us, despite all of our attempts at clinical or psychological explanation. Lest we be misunderstood, we wish to emphasize that the social adjustment or any other form of adjustment is advocated only as a great aid in stabilizing an individual patient and make him less vulnerable to recurrence of symptoms.

May we not assume that in adjusting our patients, we may alter secretion and motility in such a way as to have a favorable influence on the healing of a peptic ulcer. If we accept the role of emotional influences in the genesis of ulcer may we not accept the idea that the emotional adjustment may have a beneficial effect in the therapy?

SUMMARY

1. The importance of the individual as a whole, has not been considered sufficiently in the discussion of ulcer therapy.

2. In the normal individual who has a peptic ulcer, the stress and strain of emotional, business, social and sexual problems, interfere and aggravate the symptoms of the ulcer. If the physician can help the patient to solve some of his difficulties, such therapy is conducive to the healing of the peptic ulcer. We consider such treatment an important adjunct in the medical therapy of peptic ulcer.

3. Investigation of the emotional life of the patient is important in the differential diagnosis of peptic ulcer. It is particularly important in early and doubtful cases.

4. Since it is difficult at times to differentiate between a "healed ulcer" — with an ulcer syndrome due to an "emotional" state and an active ulcer with ulcer symptoms, an investigation of the emotional life of the individual is important for the therapy as well as diagnosis.

If patients have recurrent ulcer syndrome following apparently successful operations for ulcer, it is important to investigate the individual as a whole before attempting further medical or surgical therapy.

The Value of Cholesterol in Milk*

By

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AMONG the hundred or more recognized constituents of milk is the substance known as cholesterol. Chemically, it is a sterol with the formula, $C_{27}H_{46}O$. Quantitatively, it is one of the relatively minor components of milk, since this sterol is present in whole

milk only in amounts varying from 10 to 15 mg. per 100 c.c., or from 100 to 150 mg. of cholesterol to the quart of milk (1). There seems to be no evidence to show that cholesterol is more, or less, abundant in any particular grade or type of cow's milk. It also occurs in human milk.

Qualitatively, however, this small amount of cholesterol in milk is a matter of some significance, as indi-

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cated by the functions attributed to cholesterol in the human organism by Hurxthal and Hunt (2). These functions are ascribed as follows:

- "1. A constituent of the framework of cell because of its stability to ordinary chemical change.
- "2. A protective substance in cells, exerting its effect as:
An anti-toxic, anti-hemolytic and anti-infectious agent.
An insulator of the central nervous system.
A conditioning constituent of the skin.
- "3. A conveyor of fatty acids to and from fat deposits.
- "4. A facilitator of fat absorption."

Because of the importance of cholesterol in human metabolism and because milk is such a valuable adjunct to our diet, it seems desirable briefly to call attention to some of the more recent studies made with cholesterol showing its value in milk.

Although it has been asserted recently that a high cholesterol diet may be a factor in the development of human atherosclerosis (3), a form of arteriosclerosis characterized by degenerative changes in the connective tissue of the arterial walls, the evidence which tends to incriminate cholesterol as a cause of this condition is not impressive. Although abnormal deposits of cholesterol are consistently found in the atherosclerosis plaques, and the amount increases with the extent of the atherosclerosis, no one has as yet definitely proved that the deposition of cholesterol is the cause rather than the result of the disease. Cholesterol deposits are also found in the body in gall bladder disease, in uncontrolled diabetes, lipid nephrosis, and in a number of other morbid conditions. These deposits seem, however, to be the result of a disturbance of metabolism, and not the causative factor of the disease.

That this is so in the case of atherosclerosis is indicated by the work of Lande and Sperry (4), who compared the concentration of cholesterol in the blood serum with the lipid content of the intima of the aorta in 123 necropsy cases. They found no correlation whatever between these two factors, even in subjects with a marked degree of atherosclerosis, and reported that the average amounts of cholesterol in the serum of these persons were practically identical with those noted in normal healthy subjects.

These results, as well as other experiments, says an editorial in the *Journal of the American Medical Association* (5), "clearly indicate that factors other than the concentration of cholesterol in the blood must be involved as etiologic agents in the production of the lesions characteristic of this disease."

Atherosclerosis has been produced in the rabbit by Leary (3), by overwhelming the weak metabolic system of this animal with doses of crystalline cholesterol, but this fact does not have a human application. In the normal human body, cholesterol is both synthesized and destroyed, so that the bodily requirements for this substance are maintained in a state of equilibrium.

Although it has been alleged (3) that the use of high fat diets in the treatment of diabetes during the decade from 1920 to 1930 resulted in an increase of arteriosclerosis among these patients, no statistical

data have been adduced to support this contention. Freyberg, Newburgh and Murrill have shown, furthermore, that there is no correlation between the level of cholesterol in the blood of diabetic patients and the amount of fat in the diets (6). These investigators state that lack of control of the diabetes appears to be the major factor in the causation of hypercholesteremia in diabetic patients.

Although other sterols occur in plants, cholesterol and the related substance, ergosterol, are the only sterols found in the animal body, according to Bills (7), who has written a noteworthy review of the physiology of the sterols. Cholesterol is a constituent of body cells, being especially abundant in the brain, where it is thought to act as an insulating medium for the myelin sheaths of the nerve fibers. Cholesterol is usually associated with fat, forming esters with the fatty acids. It is present in the blood both in the form of cholesterol and as cholesterol esters, the normal range being considered to be from 120 to 230 mg. per 100 c.c. (2). Determination of blood cholesterol has a diagnostic value, although many factors may influence the quantity present.

In a recent article, Bills (8) states: "The fact that vitamin D is not a single chemical substance has only recently been recognized. The erroneous view still commonly held is that ergosterol is the parent substance, or provitamin, from which all vitamin D arises."

The irradiated ergosterol is the most thoroughly studied of the vitamin D group. Irradiation of yeast fed in proper amounts to cows produces a vitamin D in the milk, the provitamin of which is ergosterol. This is the vitamin D present in certified milk.

In the human skin, the fat is comprised of about 19 per cent cholesterol. The provitamin of cholesterol according to Bills (8) is 7-dehydro-cholesterol. Under the influence of ultraviolet light from the sun, or from artificial sources, this cholesterol is activated through its provitamin, becoming an active antirachitic agent. The provitamin in the cholesterol of milk, which is probably 7-dehydro-cholesterol (8), is changed into the antirachitic vitamin D, when subjected to irradiation. Ansbacher and Supplee (1) have shown that about 82 per cent of the cholesterol in milk is in the fat, and that the remaining 18 per cent is found largely in the milk protein, lactalbumin, with which the vitamin D produced in milk by irradiation forms a symplex, or a prosthetically-bound combination of enhanced antirachitic potency.

Compared to many other foods, milk, cream and butter are not, as has been charged (4), particularly potent sources of cholesterol. According to Bridges (9), the foods richest in this substance are egg yolk, beef and calf brains, kidney, and liver, which contain as much as 120 times the cholesterol found in whole milk. Butter, being a concentrate of milk fat, has about seven times as much cholesterol as milk, and cheese is also higher proportionately in this substance than is milk. At least 40 other foods, the cholesterol content of which is known, exceed milk in their proportions of cholesterol per 100 grams, and even such common foods as oranges, bread, lean beef, chicken, chocolate, ham, and lard equal or far exceed milk as a source of cholesterol, although the amount taken into the body would depend, of course, on the amount of

food ingested. The cholesterol content of a number of representative foods, as given by Bridges (9), is shown in the accompanying table. (Table I).

When foods containing cholesterol are eaten, all of this substance does not pass directly into the blood-

TABLE I
Cholesterol content of foods

	Me. of Cholesterol per 100 grams
Egg-yolk, duck	2617
Egg-yolk, hen	1540 2170
Brain, beef	1760 2500
Kidney, mutton	200 240
Liver, beef	200
Pancreas, calf	712
Chicken	55 525
Butter	70 220
Cheese, cream	85 55
Peas, dry	255 114
Milk, human	12
Milk, cow's	11.5 50
Cauliflower	254
Bread, white	145
Oranges	156
Lettuce	25

stream, but much of it is converted by the enzyme, cholesterase, into other substances, some of which are excreted, and some of which may go to the tissues in the form of esters. Most, if not all of the cholesterol in the body is, however, probably synthesized at an unknown site. "When all the facts are considered," says Bills (7) "it appears as likely as not that animal sterols, in so far as they are endogenous, originate in

the cells in which they occur." Vitamin D, on the other hand, is readily absorbed by the human body, and in the absence of the effects of sunlight, must be provided for infants and children in the form of appropriate food-stuffs or other materials, such as cod liver oil, other fish oils, vitamin D milk, and other substances containing one of the various forms of this vitamin.

A careful investigation of the effects of the "protective foods," defined as milk, eggs, fruit, vegetables and lettuce, on the incidence of degenerative disease was made several years ago by Langstroth (10) who reported that an analysis of the dietary histories of 501 patients revealed that the average diet contained only 12 per cent of these protective foods, and that the percentage incidence of degenerative disease increased as the percentage of protective food decreased. By means of a diet containing 70 per cent of protective food, improvement was brought about in 73 per cent of a group of 174 persons, usually by mitigation of distressing symptoms, and often by actual restoration of the integrity of the injured structure. Included among Langstroth's cases were arterio-sclerosis, as well as hypertension, myocardial degeneration, arthritis, chronic gastro-intestinal disease, diabetes, and migraine.

From the data presented, it would seem, therefore, that the small amount of cholesterol in milk is, if anything, a beneficial rather than a detrimental substance. In the light of modern knowledge, there seems to be no adequate reason for urging that normal persons attempt to curtail the amount of cholesterol in the diet (11). Certainly, there is no adequate evidence to incriminate milk as a factor in the development of any degenerative disease, including all forms of arterio-sclerosis (12).

Pure milk, whether certified or pasteurized, exhibits many dietary virtues, and so far as we know today, has no nutritional disadvantages but many advantages for the average, normal person, no matter of what age.

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Studies in Gastric Motility

The Relation of the Size of the Meal to the Gastric Emptying Time in the Dog, Using a Meal Rich in Fat and Protein

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IN a recent paper (1) it was shown that in the case of man there was a definite relation between the size of the meal and the gastric emptying time. The standard meal used in man consisted of 15 Gm. of Quaker Farina. When the subject was given a meal twice the size of the standard meal, the average gastric emptying time was prolonged 16.83 per cent over the norm. And when a meal three times the size of the standard meal was given the subject, the average prolongation of the gastric emptying time was 23.33 per cent.

While these results were not unexpected, nevertheless, as far as we are aware, this was the first time that adequately controlled work had been done on the relation of the size of the meal to the emptying time of the stomach. In the study just quoted six subjects were used; five gave consistent results, that is, the larger the meal the longer was the gastric emptying time. One subject, however, was refractory; regardless of the size of the meal (within the limits of our investigation) the gastric emptying time was not prolonged.

It was thought worth while to perform some well

in five healthy vigorous dogs. These animals had previously been kept on a prescribed diet, were fed the same time each day and were trained for this type of work. The standard meal given these dogs was one which has been used in this laboratory for a number of years (2). It consisted of: 40 Gm. of hamburger steak, 10 Gm. of dried ground bread and 50 c.c. of milk. Fifteen Gm. of barium were added for fluoroscopic purposes. A number of determinations were made (only one, however, each day) and the average figure was used for the norm.

After the control gastric emptying time had been determined, the dogs were given a meal twice the size of the standard meal. From four to six determinations were made on each animal and the average figure was used.

They were then given a meal three times the size of the standard meal; from two to four determinations were made on this type of meal and the average figure was again used.

RESULTS

The accompanying table shows the results obtained.

TABLE I
The relation of the size of the meal to the emptying time of the stomach in the dog

No.	Standard Meal			Meal twice the size of normal			Meal three the size of normal		
	No. Tests	Emptying Time In Hrs.		No. Tests	Emptying Time In Hrs.	Increase %	No. Tests	Emptying Time In Hrs.	Increase %
1.	12	6.71		4	10.09	50.69	2	12.65	86.89
2.	12	5.62		4	9.17	62.50	2	12.12	107.65
3.	10	6.27		5	9.83	57.60	4	12.77	94.29
4.	9	6.58		1	9.17	50.69	3	12.16	81.79
5.	14	6.71		5	10.75	59.70	2	13.37	99.50
Avg.	12	6.38		5	10.07	58.14	3	12.40	93.88

controlled animal experiments so as to check the results obtained in man, especially since the gastric emptying time of one of the human subjects was not altered by increasing the size of the meal ingested. It was felt too that it would be of interest to ascertain whether a meal rich in fat and protein would give a comparable result to one relatively rich in carbohydrates.

METHODS

The normal gastric emptying time was ascertained

It will be seen that in case of the standard meal the average gastric emptying time for the five animals was 6.38 hours. When a meal, however, twice the size of the standard meal was used the average gastric emptying time was 10.07 hours—an increase of 58.14 per cent. And when a meal three times the size of the standard meal was used the average gastric emptying time was 12.40 hours or an increase of 93.88 per cent.

DISCUSSION

The results obtained with dogs were more striking than those obtained in man. It is realized that the re-

sults, however, are not strictly comparable since the composition of the meals, as previously mentioned, was quite different. The Quaker farina which was used in making the observations on man has the following composition: 77.7 per cent carbohydrate; 8.8 per cent protein; 0.8 per cent fat; the remainder consists of moisture, crude fiber and ash.* The meal used in studying the dogs, however, was relatively rich in fat and protein.

The dogs gave remarkably constant results; the larger meals in all of the animals in the series produced a prolongation of the gastric emptying time. The human case which showed no difference in gastric emptying time regardless of the size of the meal (at least within the limits of our investigation) was a distinct surprise to us. It would be of interest to know if there are many such individuals. The position, size and shape of the stomach when viewed fluoroscopically, of this subject, appeared normal in every respect. The subject, furthermore, did not complain of any subjective symptoms which are commonly associated with extreme hunger.

The unusual results obtained with this individual emphasize how hazardous it is to predict the outcome of investigative work even though the work appears quite predictable.

The physiological explanation which may be given of the fact that there is not a direct proportion between the gastric emptying time and the size of the meal is that the larger meal causes a greater distension of the stomach musculature which makes the contractions more effective. It has recently been shown that smooth muscle like striated muscle is capable of contracting more efficiently when it is under a certain amount of tension.

While it is possible that the pylorus at times may play an important role in gastric emptying time, its action must not be over emphasized. Recent work (3) has confirmed the earlier work that resection of the pyloric sphincter (Rangstedt's operation) in dogs or partial parasympathetic denervation of the pylorus had no effect on the gastric emptying time. The consensus of opinion seems to be that under normal conditions the pylorus does not greatly influence the gastric emptying time.

The results obtained with the dogs certainly corroborate those obtained on man. It may be said then that a large meal no matter whether it consists mostly of carbohydrates or is rich in fat and protein is capable of delaying the gastric emptying time longer than is a smaller meal. The data in this paper also point to the fact that a large meal rich in fat and protein is capable of delaying the gastric emptying time proportionally longer than would one consisting mostly of carbohydrates. The fact, however, that man was

used as a subject for one type of meal and the dog for another type of meal makes it necessary to accept this with a certain amount of reservation. Although the results are not strictly comparable the data are most suggestive.

SUMMARY AND CONCLUSIONS

Five healthy dogs were given a standard meal consisting of 40 Gm. hamburger steak; 10 Gm. of dried poulard bread and 50 c.c. of milk together with 15 Gm. of barium sulfate. The average gastric emptying time in the five animals for this meal was 6.38 hours. When a meal twice as large was given a prolongation of 58.14 per cent in the gastric emptying time was noted and when a meal three times the size of the standard meal was given a prolongation of 93.88 per cent was produced. All the animals reacted in the same way.

In the case of man (work previously reported) in which a meal was used consisting largely of carbohydrates, a meal twice the size of the standard meal produced a prolongation of the gastric emptying time of 16.83 per cent. A meal three times the size of the latter caused a prolongation of 38.33 per cent. One individual was refractory.

It is suggested that the reason the size of the meal was not directly proportional to the gastric emptying time was that the larger meal exerted increased tension on the gastric musculature and caused more effective gastric contractions.

The conclusions which may be drawn from this work are:

- (1). The results obtained in dogs confirm those obtained in man, namely that the larger the meal the longer the gastric emptying time (within the limits of our investigations).
- (2). The first named conclusion is true whether the meal consists largely of carbohydrates or is rich in fat and protein.
- (3). The data further suggest that a large meal rich in fat and protein is capable of delaying the gastric emptying time proportionally longer than one consisting chiefly of carbohydrates. (As different animals were used with the two different meals, the data must be considered merely as suggestive).
- (4). Finally these results give further experimental evidence to the well known fact that a large meal will delay the onset of hunger contractions.

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How Does the Activity of the Cerebrum Affect the Work of the Internal Organs?

III. The Effect of Conditioned Reflexes on the Flow of Bile Through the Duodenal Ampulla

By

M. A. USSIEVICH

THAT the activity of the extra-hepatic biliary passages is influenced reflexly was established beyond doubt by the investigation of Bruno and Klodnitsky. Bruno showed in a very convincing manner how the emptying of the stomach influenced the output of bile; after extracting the stomach contents via a gastrotomy, the flow of bile decreased to zero, the flow being resumed on introducing the extracted contents into the stomach. This was confirmed later by Klodnitsky. In view of our results on the reflex connections between the cerebrum and the internal organs (Ussievich and Ussievich, Riss and Vvedensky), we have extended our investigations to determine the effect of cerebral activity on the outflow of bile, using the biliary fistula method improved by Pavlov and not removing the gall bladder.

Our observations have been made on a 25 kg. dog named "M. L." In making the biliary fistula a tongue-shaped piece of duodenum about the ampulla was excised and brought to the surface of the abdominal wall. With this modification the opening of the common duct was surrounded by muscle and mucosa, which became well insaculated in the abdominal wall.

feed the dog 600 c.c. of milk and then to subject the animal to different conditional studies. The conditioned stimuli were developed by the method of Pavlov, the salivary gland being used as an indicator and washing the mouth with 0.25 per cent HCl being used as the unconditioned stimulus.

The norms of bile output following milk were established beforehand. The curve of bile output was very uniform and the amounts excreted for a definite period (4 hrs.) was quite constant. As an example, data is presented in Table I for three different days. Data for dog "D" is also included. (Dog "D" was operated in Prof. I. P. Pavlov's laboratory and did not show scarring for ten months post-operatively). If one neglects the difference in the amounts of bile obtained in the two dogs, which difference may be due to differences in water balance, the "character" of the process of excretion is evident. The maximum rise in output occurs during the first hour, which is followed by a more or less abrupt decrease. As a rule, the maximum decrease occurs during the fourth hour after the meal. The latent period of the response varied from 5 to 7 minutes usually.

TABLE I
Bile obtained after 600 c.c. of milk

Dog "M. L."				Dog "D"			
Hour	Days			Hour	Days		
	13/1 c.c.	15/1 c.c.	17/1 c.c.		13/1 c.c.	15/1 c.c.	17/1 c.c.
1st	21.0	14.8	13.0	1st	37.0	50.0	55.0
2nd	9.0	8.3	12.0	2nd	25.0	23.0	26.0
3rd	9.0	9.9	8.6	3rd	22.0	27.0	25.0
4th	2.5	5.5	5.4	4th	15.0	16.0	14.0
Total	41.5	38.5	39.0	Total	99.0	116.0	121.0

During many months of observation scarring about the fistula, as occurred in the dogs of Bruno and Klodnitsky, did not result. The scarring in the dogs of these observers caused them to report false evidence on the rate of bile output after the ingestion of meals, as will be observed on studying the data we give later.

We chose milk as the food stimulus because milk was shown by Bruno and Klodnitsky and later by Folbort to cause a large output of bile in the shortest possible time.

The method of experimentation in brief was to

In Chart 1 the difference between our results and those of Klodnitsky is shown. The difference depends probably on the scarring or the mechanical obstruction to outflow present in Klodnitsky's animals. This assumption appears to be supported by the observations of Folbort who reported an average latent period of response to milk of from 8 to 9 minutes.

After establishing the normal output of bile in response to milk in dog "M. L." the work with conditional stimuli was started. First, we observed the influence of the formation of a conditioned stimulus to the strokes of a metronome beating with a fre-

COMPARATIVE DATA ON BILE EXCRETION WHEN FEEDING MILK IN CASES DESCRIBED BY KLODNITSKY AND IN OUR CASES

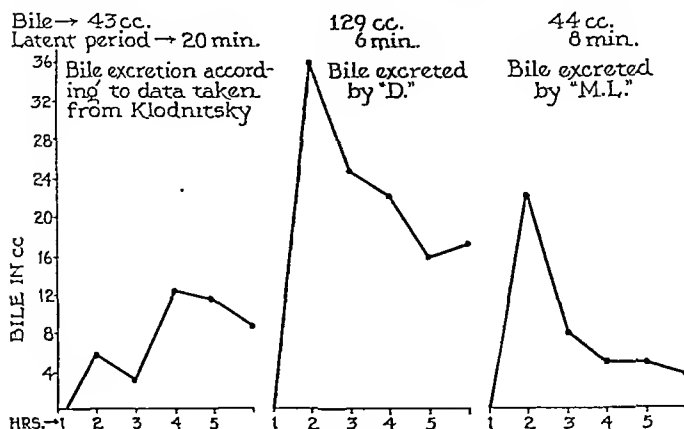


Chart 1

quency of 160 per min., M. 160. Later, when the process of bile output to the conditioned stimulus took the trend "normal" for the dog, we applied a new stimulus, i.e. differentiation to the frequency of the metronome strokes, the new stimulus beating a frequency of 60 per minute, M. 60. Still later, we studied the effect of another conditioned stimulus, namely, a special device for the mechanical stimulation of the skin through touching it (the so-called "Kasalka"), which was attached to a well-shaven area of skin on the middle surface of the left thigh. As a rule, the number of touches amounted to 24 per minute (K. 24).

From January, 1935, to the middle of June, 1936, 175 tests were conducted, which were usually made every other day; in several instances tests were made daily or at 2 or 3 day intervals. During this period the animal was in good health and maintained its weight and appetite. The animal was fed bread and milk at about 4 p. m. and nearly all the bile excreted was fed, the dog taking its bile willingly.

The character of the curve of output obtained with the control or "normal" tests enabled us to draw the conclusion that the rapidity with which the bile

reached its maximum during the first hour depends on the effect of reflex influences arising in the duodenum on the biliary ducts, when milk unchanged by gastric juice passes into the duodenum during the first few moments after feeding (Bruno and Klodnitsky). This was of great interest to us because any changes in the latent period and the character of the curve of bile output could serve as indicators of the effects our experimentation (conditional stimuli) were producing. In fact, from the first experiment of applying conditioned reflexes the amount of bile obtained decreased from an average of 40 c.c. to 28 c.c. (25 per cent) during four hours of observation. Then, the character of the curve changed until after the fourteenth experiment. During this period of change, as a matter of fact, no two tests gave similar results, the latent period being at first from 4 to 6 min. and later as long as from 12 to 24 minutes, and the period of maximum output of bile occurred in the second and sometimes the third hour instead of the first (see tests 3, 5 and 11 and Chart 2). The third test in Chart 2 is of special interest because in control tests the maximum output of bile occurred during the first 15 minute period of

THE PROCESS OF BILE EXCRETION FROM THE MOMENT OF APPLYING THE FIRST CONDITIONED STIMULUS

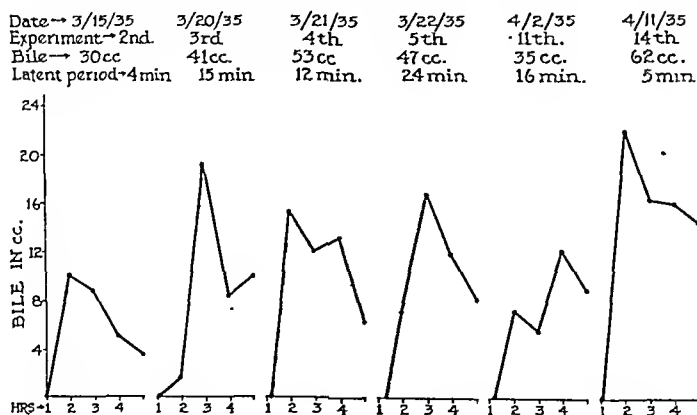


Chart 2

THE PROCESS OF BILE EXCRETION SINCE THE MOMENT
THE FORMATION OF DIFFERENTIATION BEGAN

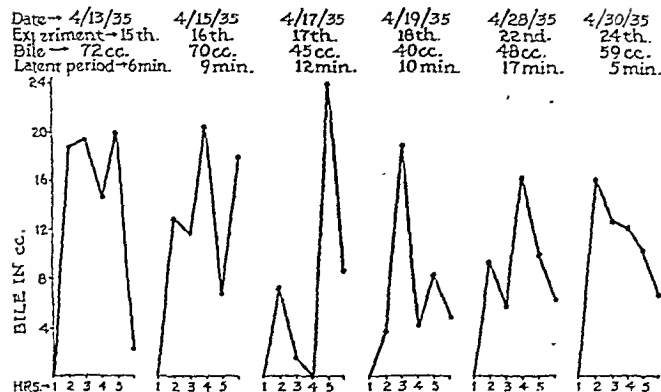


Chart 3

the first hour whereas in this test the output during the first 15 minute period was 0 c.c., the second was 5.5 c.c., the third 0 c.c. and the fourth 1.0 c.c. During the second hour the output for the first 15 minute period was 4.5 c.c., the second 5.0 c.c., the third and fourth periods together 10.0 c.c. In regard to the conditioned reflex activity during test 3, we observed considerable licking and a negative motor reaction to occur in response to the appliance of the conditioned stimulus. The *distortion of the normal curve* is also quite evident in tests 5 and 11. Thus, it is clear that the activity of the cerebral cortex initiated by the application of a conditioned stimulus reflexly influences the mechanisms concerned in the outflow of bile. The influence is not only manifest during the first few minutes of application of the conditioned stimulus, but is evident through the first and following hours.

In the fourteenth test it is to be noted that the process of bile outflow did not deviate from the normal in regard to latent period or the character of the curve. On applying in this test the conditioned stimulus M. 160 from 4 to 6 drops of parotid saliva was obtained during 20 seconds of isolated, conditioned reaction.

The effect of the application and the subsequent ap-

pearance of the "differentiated stimulus," M. 60, on outflow of bile was studied. On applying and then repeating the differentiated stimulus the normal process of bile outflow was again distorted for nine experiments. No two results were similar and the latent period was again increased. The data are shown in Chart 3 and Table II. In the first experiment (Chart 3), we observed a distorted curve. In the second experiment during the first hour, the following amounts of bile were obtained during each 15 minute period; first, 2 c.c.; second, 8 c.c.; third, 3.0 c.c.; fourth, 0 c.c. (In this experiment the value of the salivary response to the differentiated stimulus, M. 60, was greater than to the conditioned stimulus M. 160). The distortion was again repeated in the 3rd, 5th, 7th and 8th experiments, but in the 9th the normal curve of output for each 15 minute period during the first hour was restored, as well as the normal curve of hourly outflow for the four hour period (see Chart 3 and Table II). Further, the maximum outflow of bile frequently occurred in the 4th hour rather than the first, which occurred in the 1st and 3rd experiments; in the 2nd and 8th the maximum occurred in the 3rd hour and in the 4th in the 2nd hour. Thus, it is evident that when

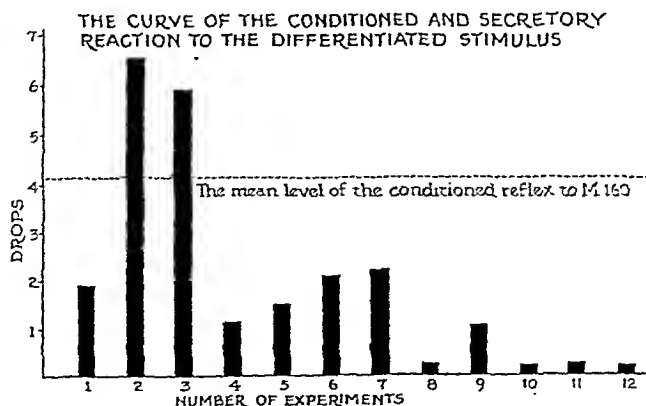


Chart 4

differentiation between the two stimuli was being formed, which required cerebral activity, the normal outflow of bile was disturbed.

As usually occurs when a differentiation between two stimuli (M. 160 and M. 60) is being formed an undulating course is observed. In regard to this, at-

having been fed to cause a flow of bile. It was found that the application of the conditioned stimulus, M. 160, definitely altered the latent period and the characteristics of the curve of response of bile outflow after milk for a period of fourteen tests, after which a normal response occurred. The introduction of a

TABLE II

The bile output for each 15 minute period during the first hour when the "differentiated" stimulus M.60 was applied

No. of Experiments	1st 15 Min. Period c.c.	2nd 15 Min. Period c.c.	3rd 15 Min. Period c.c.	4th 15 Min. Period c.c.	Remarks
3rd	4	3	0	0.5	Salivary response was much higher than to conditioned stim. M.160.
5th	0	7	5	2	Incomplete discrimination between conditioned and "diff." stimuli.
7th	5	9	8	1	Practically no discrimination.
8th	0	4	2	4	Complete discrimination between the two types of stimuli.
9th	7	8	3	2	Weak disinhibition.
10th	5	5	4	3	Complete and steady discrimination.

tention should be directed to Chart 4, which shows the salivary response. In the first experiment a lower secretory effect is obtained to the "differentiated" than to the conditioned stimulus. During the two following experiments an increase was obtained. In the 4th experiment when applying the "differentiated" stimulus for the 7th time, we observed no secretion; but we observed a residue of the motor reaction characteristic of the conditioned stimulus (dog licks its lips, gnaws the device for applying the acid, and turns its head aside as though acid had actually been applied) followed by pronounced reactions of an inhibitory character. The 5th and 6th experiments yielded somewhat similar results. Disinhibition (inhibition of inhibition) was observed in the 7th experiment. The first clear evidence of discrimination between the two stimuli was observed in the 8th experiment. A slight disinhibition occurred during the 9th and a complete and steady discrimination began with the 10th experiment.

When the conditioned reflex activity shows the greatest range, the deviations from the normal output of bile are greatest. For example, in experiment 1, Chart 3, when the stimulus M. 60 gives a lowered conditioned reflex (Chart 4), the bile output is at a high level for four hours and the maximum is during the fourth hour. In experiments 2 and 5, the output to M. 60 is excessively high and of a character never observed in the dog before or after. The results of experiment 3 are of special interest because of the marked irregularity in bile output.

DISCUSSION

The effect of cerebral activity on the outflow of bile has been studied by the application of the method of conditioned reflexes on a dog with a permanent biliary fistula so prepared as to avoid artifacts due to scarring or mechanical obstruction of the ampulla of the common duct. The normal outflow of bile from the fistula on the ingestion of 600 c.c. of milk was determined. Then, the salivary gland was conditioned to a stimulus, the stimulus being a metronome beating at a frequency of 160 per minute, the milk, of course,

stimulus (M. 60) that had to be differentiated from the conditioned stimulus (M. 160) caused a marked distortion of the curve of the outflow of bile from the fistula for a preliminary period of nine experiments.

These results show that the state of cortical activity, the process of "learning," has a definite effect on the outflow of bile from the biliary passages, which must be due to a true "dyskinesia" (Bergmann, Westphal, Ivy and others). This may be considered, as others have previously done as evidence, of the importance of dyskinesia in the etiology of diseases of and symptoms from the gall bladder and biliary ducts.

The changes in the outflow of bile, or the dyskinesia may be related to changes in gastric secretion or motility, since we found in our previous experiments on a Pavlov pouch that gastric secretion was decreased during the development of a conditioned reflex, and it is known that biliary outflow is related to gastric secretion and motility. Either this explanation holds or the musculature of the extra-hepatic biliary passages is directly affected through its extrinsic nerves. It is suspected that both influences operate to effect the changes observed.

CONCLUSIONS

1. During the formation of a conditioned reflex the volume outflow of bile from the biliary passages in response to the ingestion of milk is reduced, the latent period of outflow of bile in response to milk is lengthened, and the characteristics of the curve during the first and succeeding three hours is distorted from the normal.

2. The application of a stimulus that must be differentiated from the conditioned stimulus markedly distorted the normal response to milk. This is best explained by assuming that a true biliary tract dyskinesia occurred.

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The Prevention or Healing of Experimental Peptic Ulcer in Mann-Williamson Dogs with the Anterior Pituitary-Like Hormone (Antuitrin-S)

A Preliminary Report

By

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ONE of us (D. J. S.) has made the clinical observation that pregnancy has a beneficial effect upon peptic ulcer. Women who have active peptic ulcers, both clinically and roentgenologically become symptom-free with the onset of pregnancy. Activation of a pre-existing ulcer during pregnancy is rare. Discussion with several experienced obstetricians confirmed this; they uniformly did not remember any patient with ulcer or its complications during pregnancy. The records at Harper Hospital for ten years did not show any case of admission of a pregnant woman with active ulcer symptoms or complications.

A review of the literature confirmed this impression.

Hurst and Stewart (1) state: "There is no doubt that pregnancy exerts a favorable influence on the symptoms of ulcer, especially of the stomach, and in some cases it appears to lead to actual healing apart from any specific treatment."

Crohn (2) says in a foot note: "Ulcer cases in women usually do very well during pregnancy. The

ulcer usually goes into intermission and gives few, if any, symptoms of activity."

Other similar reported observations are:

Adair and Stieglitz (3): "Fortunately, patients who have had symptoms of peptic ulcer before pregnancy are usually comfortable during pregnancy, and the ulcer becomes inactive."

"Patients with visceroptosis commonly complain of symptoms referable to the duodenum. Pregnancy usually causes an improvement or disappearance of these obstructive like signs. Duodenal ulcer is very uncommon during pregnancy."

Anderodias (4): "Pregnancy does not aggravate gastric ulcer and delivery has little effect upon its course."

Balint (5): "It is a clinical experience not at all rare that ulcer improves during pregnancy. The symptoms cease and very frequently the ulcer also heals."

Westphal (6): "There is distinct recession of ulcer symptoms in pregnancy."

Blakeley (7): "Some painful intra-abdominal conditions may be improved by or during pregnancy—abdominal hernia, visceroptosis, gastric ulcer."

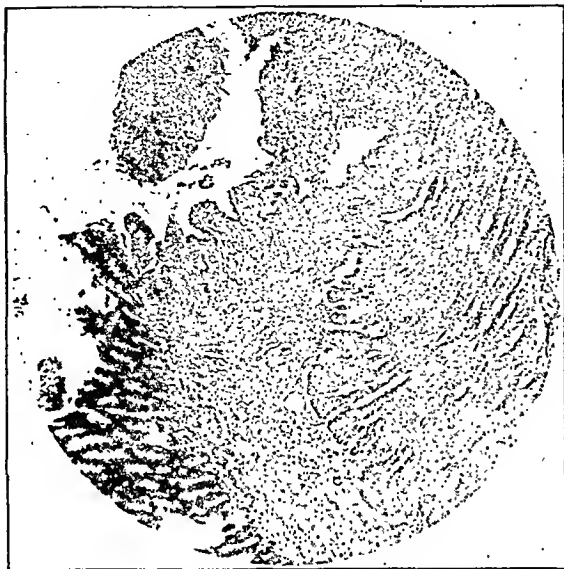


Dog No. 110 (c); high power showing beginning of epithelial covering of the ulcer at its edge; fibroblastic proliferation at base, and newly formed blood vessels.



Dog No. 120 (b); Proliferative changes at edge of ulcer; fibroblastic proliferation at base with newly formed blood vessels.

*From the Surgical Laboratory, Harper Hospital. Aided by a grant from the Mendelson Fund. Theelin and Antuitrin-S were furnished through the courtesy of Parke-Davis & Company.



Dog No. 120 (a) died 44 days post-operatively. One c.c. of Antuitrin-S (anterior pituitary-like hormone) was given from the day of operation to the day of death. Photomicrograph showing epithelial covering at edge of ulcer. Attempt at healing.

Mulsoy and Brown (8): Refer to the "rare complication of peptic ulcer in pregnancy."

Adair and Stieglitz (3): "In twenty years at the Minnesota General Hospital no case of peptic ulcer in pregnancy had to be treated."

Szenes (9) was impressed with the rarity of operations for peptic ulcer during pregnancy while serving as assistant in the large gastric clinics of von Eiselsberg and Finsterer.

Mussey (10) of the Mayo Clinic reported 370 opera-

TABLE I
Effect of Mann-Williamson operation on untreated dogs

Dog	P.O. Duration of life (days)	Results
24	31	Perforated ulcer.
39	113	Perforated ulcer.
43	51	Perforated ulcer.
45	66	Three ulcers.
50	38	Ulcer.
64	13	Perforated ulcer.
65	46	Large ulcer.
61	98	Perforated ulcer.
66	74	Perforated ulcer.
60	99	Perforated ulcer.
58	113	Perforated ulcer.
64	13	Perforated ulcer.
100% of dogs died with ulcer.		
76% of dogs died of perforated ulcers.		

tions of necessity during pregnancy over a period of ten years: Two were for peptic ulcer.

The reasons given are various:

(1). The support offered to the stomach by the rising uterus. (Hurst and Stewart; Adair and Stieglitz; Blakeley; Szenes). The strain on the lesser curvature should thereby be relieved, thus improving local circulation. (Hurst and Stewart).

(2). The blood and tissues tend to become more alkaline. (Balint).

(3). Increased fat padding in pregnant women. (Szenes).

(4). A patient anemic and in poor health from ulcer is unlikely to become pregnant.

This rarity of ulcer symptoms in pregnancy is all the more striking, since "in general, the pregnant abdomen seems to be more prone to painful sensations than the non-pregnant." (Blakeley).

It is common clinical knowledge that disease of the liver and bile passages, ptosis or obstruction of the intestinal and urinary tracts and inflammatory processes are all made worse by pregnancy. The rise and pressure of the gravid uterus has been held responsible for many and varied symptoms.



Dog No. 126 died 60 days post-operatively. One c.c. of Antuitrin-S (anterior pituitary-like hormone) was injected daily beginning with the day of operation to the day of death. No ulcer. The gastrojejunal stoma is shown in the photograph.



Dog No. 43; untreated (*control*); died 51 days post-operatively. Perforated ulcer.

ENDOCRINOLOGICAL RELATIONSHIP

Szenes (9) having found twelve gastric and seven duodenal ulcers in pregnant women, and having carefully reviewed the literature up to 1924 made these observations:

(a). Women who have never become pregnant come to operation for ulcer at an earlier average age than those who have had one or more pregnancies.

(b). Ulcer patients who get better during pregnancy are those who have little or no vomiting, while those who do not improve or get worse have frequent vomiting.

(c). In only 10% of cases was the onset of ulcer symptoms at the time of the menopause. "This small percentage speaks for the fact that the ovarian function plays a role in the genesis of ulcer."

Winkelstein (11) in 1935 observed that ulceration of abdominal wall occurred about the opening of Pavlov pouches in two of his experimental dogs. These healed during oestrus. Another ulceration which started during pregnancy was healed after ten daily injections of theelin (present actively during oes-

trus). Lactation again broke open the ulceration, and it was again healed with Theelin. Then using antuitrin-S injections, it promptly broke open again. There seemed to be no relation between the secretory activity of the pouch and the amount of ulceration.

He thought these results significant, and that they might have a possible relationship to peptic ulcer in man, and perhaps to the overwhelming preponderance of human ulcer in the male.

Thus, there are several brief reports of pregnancy having a beneficial influence upon peptic ulcer. Various explanations have been offered. Szenes (9) in 1924 and Winkelstein (11) in 1935 suggested that there may be an association between the ovarian function and peptic ulcer.

METHOD OF STUDY

On the basis of the above impressions we decided to test the effect of the hormones which are found abundantly during pregnancy, on experimental jejunal ulcers in dogs.

The standard Mann-Williamson operation (12) was performed. The pylorus was sectioned and the distal end was inverted. The open end of the stomach was anastomosed to the jejunum 10 cm. beyond Treitz ligament (after dividing the jejunum at this point). The end of the jejunum draining the duodenal juices was then anastomosed to the terminal ileum about 20 to 30 cm. above the ileo-cecal valve. Fine silk was used throughout, with no clamps. The dogs were starved 24-28 hours before operation. Ether anaesthesia was used. They were given water as tolerated



Dog No. 78 died 42 days post-operatively. One thousand international units of theelin in oil were injected daily beginning with the day of operation to the day of death. Perforated ulcer.



Dog No. 119 died 57 days post-operatively. One c.c. of *antuitrin-S* (anterior pituitary-like hormone) was injected daily beginning with the day of operation to the day of death. No ulcer.

for four days post-operatively (plus saline subcutaneously as needed, 3-4 days) and then placed on a diet consisting of finely chopped hamburger, bread and milk. The reason for this was to allow no roughage.

The Mann-Williamson operation of surgical duodenal drainage produces ulcer in 95-100% of animals. Although many investigators have worked with these ulcers, no method or procedure has so far been done which completely heals or prevents the development of these ulcers (except fundusectomy with high-purine, high-carbohydrate, and high-vitamine diet reported by Fauley and Ivy (13)). With the latter exception the dogs invariably die, usually within two or three months after the operation. Post mortem examination shows a chronic ulcer in the jejunum, always opposite the stoma, $\frac{3}{4}$ -1 cm beyond the suture line where the unprotected jejunal mucosa first comes in contact with the acid gastric stream. There is no evidence of healing.* There is marked bleeding and frequently perforation of all the coats of the jejunum.

Previously we (14) reported that 12 control dogs who had had the Mann-Williamson operation developed typical jejunal ulcer, and 13 dogs treated with histidine also developed jejunal ulcers.

To determine the effect of sex hormones found abundantly during pregnancy upon Mann-Williamson ulcers we selected theelin (estrin) and antuitrin-S for two series of dogs.

Theelin, as is well known, is a hormone produced

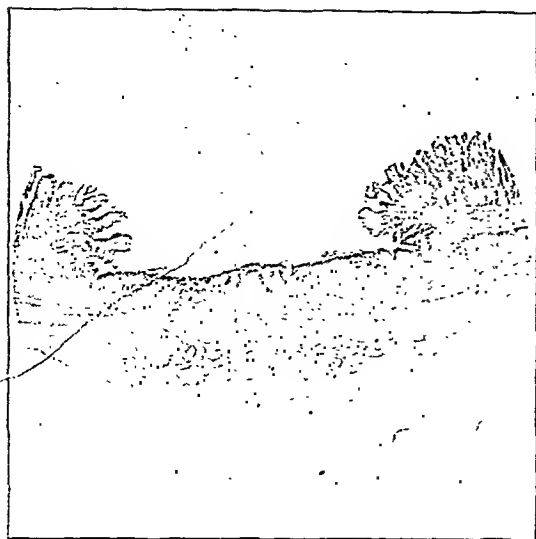
by the Graafian follicle and acts upon the endometrium stimulating its development up to the interval state (i.e. the progesterin or degenerative phase) of the menstrual cycle. Normally, according to Gustavson, Hays and Wood (15), a woman excretes 13,000 international units of theelin during a month. This excretion varies and they found a peak of 900 international units occurring in a single day during the cycle. During pregnancy the excretion of estrogenic substances in the urine increases as gestation progresses and most investigators at the present time consider that the peak excretion in the latter part of the third trimester will range from 150,000 to 200,000 international units per liter of urine.

Antuitrin-S is an anterior pituitary-like hormone believed to be produced in large amounts by the chorion of the developing embryo. It is the presence of large amounts of the pituitary-like substance in the urine which is the basis of the pregnancy tests. Normally, according to Wolf (16), the urine of non-pregnant women (except at the inter-menstrual period) and of men contains very little pituitary-like hormone; but after the second day of the first missed period in a pregnant woman it is already present in sufficient quantities to get a positive Asheim-Zondek test. The amount generally increases until the 30th to 36th day when, as shown by Evans, Kohls and Wonder (17), as much as 130,000 to 150,000 rat units (or even a million rat units) may be excreted in urine within 24 hours. There is a precipitate decrease immediately after the peak excretion but a level of 5-10



Dog No 110 died 106 days post-operatively. One c.c. of *antuitrin-S* (anterior pituitary-like hormone) was injected daily beginning with the day of operation to the day of death. Superficial ulcer.

*"I should say that there is no evidence of healing in dogs dying within 12 weeks postoperatively. In dogs surviving longer, evidence of healing may be observed at some point about the edge of the ulcer." Ivy, A. C. Personal Communication.



Section of ulcer found in Dog No. 110; (b) base of ulcer rests on outer layer of muscle and is composed of fibroblasts and newly formed blood vessels with a thin pyogenic membrane over surface. The epithelial cells at periphery of the ulcer are in good condition, showing beginning covering of the ulcer just at its edges.

thousand rat units daily is maintained until the termination of pregnancy.

Fifteen Mann-Williamson dogs were injected subcutaneously daily with 1,000 international units of theelin in oil from the date of operation to the date of death. Fifteen Mann-Williamson dogs were injected daily with 1 c.c. of antuitrin-S (100 rat units) from the date of operation to the date of death. The

diet used was the same for both of these series as well as for the control series. The dogs were not sacrificed except occasionally when found in extreme moribund condition and death was expected during the night. All dogs died either of peritonitis following perforation of the ulcer or of a disturbance in nutrition as a result of the duodenal contents being diverted into the terminal ulcer.

RESULTS

(1). Of the twelve Mann-Williamson control dogs all died with typical jejunal ulcers within 16.1 weeks. Nine (75%) died of peritonitis (following perforation) or hemorrhage. None of the ulcers showed evidence of healing. (Table I).

(2). Of the fifteen dogs injected with theelin all developed the typical jejunal ulcers. All died within 10.6 weeks from the date of operation. Eleven (73%) died of peritonitis (following perforation) or hemorrhage. None of the ulcers showed evidence of healing. (Table II).

(3). Of the fifteen Mann-Williamson dogs treated with antuitrin-S seven (47%) died with jejunal ulcers. Four of these (27% of the total) showed definite evidence of healing microscopically, i.e. fibroblastic proliferation, newly formed blood vessels, a very thin pyogenic membrane, and early covering of the ulcer surface at the margin. Only one of the seven (7%) died of a perforated ulcer. The remaining eight (53%) showed no gross or microscopic evidence of jejunal ulcers (Tables III and IV). The dogs died of inanition as a result of the duodenal contents being diverted into the terminal ileum.

Antuitrin-S, therefore, had either prevented ulcer formation, completely healed the ulcer, or caused healing to take place in (80% of the Mann-Williamson dogs. Five more Mann-Williamson dogs are still alive and are being treated with antuitrin-S. One is still

TABLE II
Effect of Theelin on Mann-Williamson ulcers

Dog	P.O. Duration of life (days)	Results
78	42	Perforated ulcer.
79	45	Perforated ulcer.
80	53	Perforated ulcer.
82	38	Perforated ulcer.
83	74	Perforated ulcer.
85	62	Ulcer.
89	48	Perforated ulcer.
99	46	Ulcer.
102	38	Ulcer.
103	22	Perforated ulcer.
105	18	Perforated ulcer.
106	49	Ulcer.
108	16	Perforated ulcer.
109	61	Perforated ulcer.
104	13	Perforated ulcer.
100% of dogs died with ulcer.		
73% of dogs died of perforated ulcers.		

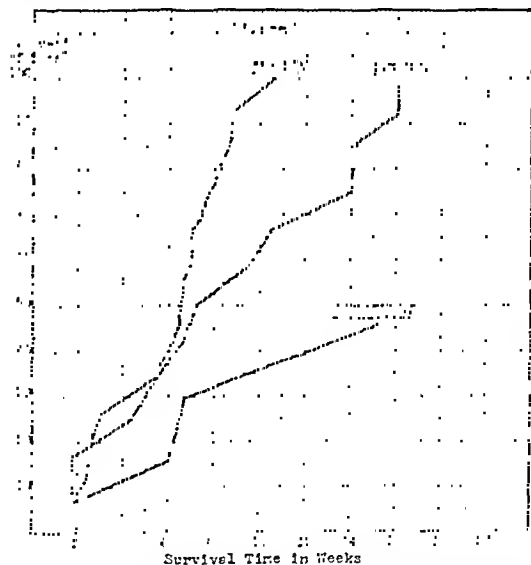


Fig. 1. The survival time of the Antuitrin-S treated dogs is longer than that of either the control series of the theelin treated series. Five dogs treated with Antuitrin-S are still alive. (See Table III).

alive 41 weeks post-operatively; two, 29 weeks post-operatively; one 14, and one 6 weeks post-operatively.

The antuitrin-S ulcers were different than any we had previously seen. When present, they were small and superficial. There was apparent evidence of heal-

TABLE III
Effect of Antuitrin-S on Mann-Williamson ulcers

Dog	P.O. Duration of life (days)	Results
90	72	No ulcer.
91	46	Perforated ulcer.
92	52	No ulcer.
97	49	No ulcer.
101	24	No ulcer.
110	106	Small ulcer—healing.
114	58	No ulcer.
116	37	No ulcer.
117	79	Large superficial ulcer.
119	57	No ulcer.
120	44	Two ulcers—healing.
121	43	Two small ulcers.
125	16	Ulcer—healing.
125	60	No ulcer.
130	25	Ulcer—healing.
47% of dogs died with ulcer. In 4 of the seven dogs, the ulcers showed evidence of healing. 7% of dogs died of perforated ulcer. 53% of dogs failed to show ulcers.		
107	—	Alive 201 days post-operatively.
111	—	Alive 286 days post-operatively.
123	—	Alive 206 days post-operatively.
124	—	Alive 100 days post-operatively.
128	—	Alive 42 days post-operatively.

ing macroscopically. In only one instance did the ulcer perforate through all the coats. The jejunum had the appearance of being healthier than in the previous controls.

Fig. 1 shows three curves representing the percentage survival-time of the untreated (controls), theelin treated and antuitrin-S treated Mann-Williamson dogs. These were constructed similar to those of Ivy's (18) in interpreting the prophylactic effectiveness of various therapeutic measures in experimental peptic ulcer. It shows that 100% of the untreated (control) and theelin treated dogs died with ulcers within 16.1 and 10.6 weeks respectively. Of those treated with antuitrin-S only 47% of the dogs died with ulcer.*

DISCUSSION

DeBaakey (19), reporting his results on the relative protective value of alkaline duodenal juices in experimental ulcers in dogs concludes that "of all the constituents of the alkaline duodenal juices, bile has the most significant and effective influence in preventing the formation of jejunal ulcer; the duodenal secretion, the succus entericus, is the least important, and the pancreatic juice is midway between the two in this respect."

In the Mann-Williamson dogs the duodenum and its alkaline contents is diverted into the terminal ileum, thus

depriving the stomach and jejunum of all the alkaline duodenal fluids (including the bile and pancreatic juice). Of our untreated (control), theelin treated, and histidine treated Mann-Williamson dogs all developed ulcers. In our antuitrin-S-treated-Mann-Williamson dogs 53% did not develop ulcers and an additional 27% though having ulcers showed definite evidence of healing—this, in spite of the absence of the alkaline duodenal fluids, bile and pancreatic juice. Further work is to be done to determine the effect of antuitrin-S on gastric acidity, gastro-intestinal motility and tissue healing. It is also important to determine the effect of the peptone fraction (to which the anterior pituitary-like hormone is attached) on Mann-Williamson ulcers.

On the basis of the clinical observation (that pregnancy has a beneficial effect on peptic ulcer) and on the above experimental results (that antuitrin-S has apparently a preventive or inhibitive effect on Mann-Williamson ulcers) the improvement in ulcer noted during pregnancy may have a relationship to the large amounts of antuitrin-S present in the body at this time.

A lack or deficiency of anterior pituitary-like hormone or decreased production of the gonadotropic hormone of the anterior pituitary gland in the non-pregnant subject may be a factor in the genesis of peptic ulcer in man. The anterior hypophysis is normally active until the stage of post-adolescence is reached, prior to which peptic ulcer is rare. Furthermore, the lower incidence of peptic ulcer in the female, contrasted with a very high incidence in the male during maturity, might be explained by a greater glandular activity in the female reproductive zone, due to her cyclic physiologic phenomena. In the female, the reproductive cycle may serve in some measure as a preventive of peptic ulcer.

SUMMARY

(1). There is clinical evidence that ulcer and its complications are infrequent during pregnancy.

(2). The attempt was made to prevent or heal experimental ulcers (Mann-Williamson dogs) by daily injections of estrogenic and gonadotropic hormones which are known to be excreted in greatly increased amounts during pregnancy.

(3). Twelve untreated (control) Mann-Williamson dogs all died with typical jejunal ulcers. 75% died of peritonitis following perforation. There was no evidence of healing.

(4). Fifteen Mann-Williamson dogs treated with theelin all died with typical jejunal ulcers. 73% died of peritonitis following perforation. There was no evidence of healing. These dogs died sooner than the control dogs which appears to indicate that theelin accelerates perforation as compared with the control series.

(5). Fifteen Mann-Williamson dogs were treated with antuitrin-S. 53% of the dogs failed to show ulcer at post-

TABLE IV
The prevention or healing of Mann-Williamson ulcers with Theelin and Antuitrin-S

	No. of Dogs	Died with Jejunal ulcer	Death due to Perforation or Hemorrhage	Prevention of Ulcer	Definite Healing of Ulcer
Control	12	12 (100%)	9 (75%)	0	0
Theelin	15	15 (100%)	11 (73%)	0	0
Antuitrin-S	15*	7 (47%)	1 (7%)	8 (53%)	4 (27%)
80%					

*Five more Mann-Williamson dogs treated with Antuitrin-S are still living. See Table III.

*The horizontal line in Fig. 1 indicates the survival time in weeks. The vertical line represents the percentage of the total animals, which died and post mortem showed ulcer.

mortem examination (death due to inanition). Of the seven dogs that died with ulcer, four (27% of the total) showed definite evidence of healing microscopically, as fibroblasts proliferation, newly formed blood vessels, a thin pyrogenic membrane, and early covering of the ulcer surface at the margins. A total of 80% of the Mann-Williamson dogs either had their ulcers prevented, healed, or healing during antuitrin-S treatment. Only one died of a perforated ulcer. (See Table IV).

(6). The improvement in peptic ulcer noted during

pregnancy may have a relationship to the large amounts of antuitrin-S present in the body at this time.

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Further Attempts to Produce Achlorhydria

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IN a previous report we have indicated the desirability of producing achlorhydria experimentally (1). We have continued the investigation with the study of various other substances including:

- I. Organo-therapeutic products
 - A. Theelin
 - B. Emmenin
 - C. Pitressin and Pituitrin
 - D. Pepsin
 - E. Larostidin
- II. Drugs acting by remote effect on body chemistry
 - A. Potassium citrate
 - B. Monobasic sodium phosphate
 - C. Sodium thiosulphate
- III. Dyes
 - A. Indigo Carmine
 - B. Toluidine Blue
 - C. Methylene Blue
 - D. Congo Red
 - E. Eosin

IV. Local irritants

- A. Silver nitrate
- B. Sodium selenite
- C. Cobalt acetate

METHOD OF EXPERIMENTATION

Experiments were performed on dogs with Pavlov pouches and with patients with chronic duodenal ulcer. Two types of gastric stimulants were used—food and histamine. Fractional test meals of crackers and water, and subcutaneous injections of 0.5 mgm. of histamine (ergamine acid phosphate, "Imido-Roche") were employed as the gastric secretory stimuli in fasting patients. The dogs were fed 200 grams of meat, 200 c.c. of milk, and 200 c.c. of water, or given 1 mgm. of histamine subcutaneously. Samples were withdrawn from the stomach of the patients every ten minutes for two hours after the test meal or histamine injection, and for seven hours from the pouches of the dogs after a meal, and for two hours after histamine. Control samples were taken before any procedure was instituted. The acidity of the stomach contents was determined by titration with

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TABLE I

A comparison of the gastric secretory response to a meal and histamine before and after two thousand units of Theelin daily for one month

	Total Volume Output c.c.	Maximum Free Acid Clinical Units	Maximum Total Acid Clinical Units	Total Acid Output mgms.
Meal				
Average of 12 control experiments on dog No. 1	130	145	168	688
Average of 14 experiments on dog No. 1 during Theelin administration	135	149	157	673
Average of 12 control experiments of dog No. 2	117	132	155	675
Average of 14 experiments on dog No. 2 during Theelin administration	122	136	144	660
Histamine				
Average of 12 control experiments on dog No. 1	20	136	146	76
Average of 18 experiments on dog No. 1 during Theelin administration	22	127	140	78
Average of 12 control experiments on dog No. 2	14	130	140	71
Average of 18 experiments on dog No. 2 during Theelin	16	120	132	75

0.1% Normal NaOH, Topfer's reagent and phenolphthalein being used as indicators.

ORGANOTHERAPY PRODUCTS

Certain endocrine products have been suggested for use in the treatment of peptic ulcer on the basis of theoretical deductions. Strauss and Castle (2) reported a decline in gastric acidity in women during the second trimester of pregnancy. During the last month of pregnancy the acidity levels rose to those observed in the third month. Van Zant and Alvarez (3) reported tendency for gastric acidity to be low during menstruation. Hellebrandt and Brogdon (4) using daily alcohol test meals observed a marked decrease of free hydrochloric acid, but relatively little change in total acidity, during a normal menstrual period. The corpus luteum involutes about the eighth month of pregnancy. The luteal hormone is secreted in substantial amounts during the early months of pregnancy, and in the last half of the menstrual cycle. Theoretically the corpus luteum might be responsible for the diminution in acidity observed during pregnancy and menstruation. Manville and Monroe (5)

noticed that pregnant dogs did not give the normal gastric secretory response to histamine. They gave dogs corpus luteum without observing an inhibition of the gastric secretory response to pilocarpine.

THEELIN

Winkelstein (6) reported that injections of theelin hastened the healing of abdominal wall ulcers occurring about the opening of Pavlov pouches in dogs. He suggested that theelin might also be of value in the treatment of peptic ulcer. We were interested in knowing whether theelin might influence the gastric secretory response to histamine or to a meal in dogs and in patients with duodenal ulcer.

Two thousand units of theelin were given daily for one month intramuscularly to two dogs (10-12 kilos in bd. wt.) with Pavlov pouches. The secretory response to a meal and to histamine was unchanged by the administration of theelin (Table I). The benefit in the healing of abdominal wall ulcers in the dogs with Pavlov pouches (observed by Winkelstein) apparently was not due to a diminution of acid secretion.

TABLE II

The effect of emmenin on the gastric secretory response to histamine and a fractional test meal. (Average results to two patients)

	Total Volume Output c.c.	Maximum Free Acid Clinical Units	Maximum Total Acid Clinical Units	Total Acid Output mgms.
Meal				
Before emmenin		60	102	
After 12 c.c. emmenin daily for 14 days		56	72	
Histamine				
Controls	215	95	119	339
Response to histamine after 12 c.c. emmenin daily for 14 days	90	102	122	168

TABLE III

The effect of daily injection of 5 c.c. of larostidin on the secretory response of the Pavlov pouch to a meal

	Total Volume Output c.c.	Maximum Free Acid Clinical Units	Maximum Total Acid Clinical Units	Total Acid Output mgms.
Average of 10 control experiments on dog No. 1	130	145	168	661
Average of 10 experiments on dog No. 1 during and after daily larostidin injections for 1 month	128	144	164	662
Average of 10 control experiments on dog No. 2	117	136	155	648
Average of 10 experiments on dog No. 2 during and after daily larostidin injections for 1 month	116	134	151	644

The effect of theelin also was studied on a patient with duodenal ulcer who was having menopausal symptoms. Ten thousand units of theelin were given intramuscularly every day for twenty days. The gastric secretory response to a fractional test meal and to histamine was not modified by the theelin treatment.

EMMENIN

Collip (7) discovered emmenin, another substance having a powerful estrogenic potency. Our experience on the comparative effects of emmenin and theelin on menstrual edema (8) led us to believe that there also might be further physiologic differentiation of these substances in their effects on the gastric secretion. We compared the results of fractional test meals and histamine before and after giving 12 c.c. of emmenin daily for two weeks to two patients with duodenal ulcer. The maximum free and total acidity values of repeated tests were essentially unchanged but the volume and milligrams of acid secreted during the test period were somewhat diminished (Table II).

PITUITRIN AND PITRESSIN

Pituitary extract (posterior lobe) was reported to have brilliant effects in gastric hyperacidity and peptic ulcer by Drouet and Simonin (9). They claim to have demonstrated that pituitary extract has the definite effect of diminishing gastric acidity. On the other hand Dodds, Noble and Smith (10) reported that the posterior lobe of the pituitary contains a substance which, when injected, induces a severe lesion of the acid-bearing area of the stomach in rats. They suggested that either there was a direct toxic action on the cells or that the secretion of hydrochloric acid was stimulated to a damaging extent.

Because of these interesting and diametrically opposite findings of the action of the posterior lobe, pituitary extract, we were interested in studying the effect of subcutaneous injections of pituitrin and

pitressin on the gastric secretory response of the Pavlov pouch to a meal.

Pituitrin and pitressin in 1 c.c. doses (Parke Davis) were given by subcutaneous injections to two dogs with Pavlov pouches for two weeks. There was no essential change in the gastric secretory response to a meal.

PEPSIN

Glaessner (11) and others (12) have reported benefit to accrue in the treatment of gastric and duodenal ulcers, and a diminution in gastric acidity from the subcutaneous injection of pepsin. We obtained ampules of this substance, supposedly identical with that used by Glaessner. The pepsin was given to two dogs with Pavlov pouches in increasing amounts up to 3 c.c. daily for three and one-half months. We observed no change in the secretory response of the Pavlov pouches to a meal. We also observed no change in the peptic activity of the gastric juice as measured by the Metz test. We realize that negative results in dogs necessarily do not negate positive findings in patients with peptic ulcer.

HISTIDINE MONOHYDROCHLORIDE

Weiss and Aron (13) in 1933 introduced the parenteral injections of histidine hydrochloride in the treatment of peptic ulcer. A number of reports concerning the efficacy of this treatment have since appeared. We considered it pertinent to investigate the effect of histidine on the gastric secretory response of dogs and patients with duodenal ulcer to histamine and to a meal.

Five c.c. of larostidin (4% solution of laevo-histidine monohydrochloride) were injected daily intramuscularly into two dogs for one month. There was essentially no change in the gastric secretory response to a meal or to histamine after larostidin injections (Tables III and IV).

To study the effects of histidine on the acid secre-

TABLE IV

The effect of larostidin on the secretory response of the Pavlov pouch to histamine

	Total Volume Output c.c.	Maximum Free Acid Clinical Units	Maximum Total Acid Clinical Units	Total Acid Output mgms.
Average of 10 control experiments on dog No. 1	22	131	144	83
Average of 10 experiments on dog No. 1 during and after larostidin injections for one month	22	125	142	81
Average of 10 control experiments on dog No. 2	18	126	140	80
Average of 10 experiments on dog No. 2 during and after larostidin injections for one month	18	122	135	79

TABLE V

The effect of histidine (larostidin) on gastric secretory response to histamine in three patients with duodenal ulcer

	Total Volume Output c.c. 2 hrs.	Maximum Free Acid Clinical Units	Maximum Total Acid Clinical Units	Total Acid Output mgms.
Average of controls	433	78	90	608
After 30 injections of histidine	625	62	78	812

tion of man, tests were made on three patients with duodenal ulcer by giving injections of 5 c.c. larostidin daily by intramuscular injection for one month, and comparing the gastric secretory response to histamine in three experiments before beginning larostidin and three experiments at the completion of the course of treatment. There was a slight decrease in the maximum free and total acidity titres, but an increase in the volume and total milligrams of acid output in response to histamine stimulation. These changes are without significance (Table V).

A patient with duodenal ulcer with "continuous hypersecretion" (an active secretion while fasting) was studied before and after thirty injections of histidine without any gastric secretory stimulus. The fasting stomach contents were somewhat decreased in acidity, but the volume or rate of secretion was greater (Table VI).

If histidine is of value in the treatment of peptic ulcer, its value apparently is not due to a diminution of acid secretion.

DRUGS ACTING BY REMOTE EFFECT ON BODY CHEMISTRY

Most studies of the effect of alkalis on gastric secretion have been concerned with sodium bicarbonate. Some investigators have thought that sodium bicarbonate not only neutralizes the hydrochloric acid in the stomach, but also reduces the amount of acid secreted in the stomach. Boyd (14) demonstrated that massive doses of sodium bicarbonate depressed gastric secretion in dogs. With doses within the limits of ordinary antacid medication the secretory response to a meal was slightly greater than without the alkali. He also stated that massive doses depressed the gastric secretory response to histamine, whereas doses up to one gram per kilogram of body weight did not affect the secretory response unless given in five per cent concentration.

We thought that since sodium bicarbonate had a local neutralizing effect in the stomach, we would study the effects of potassium citrate, in which the local action is absent, but the systemic action is that

of an alkali. Potassium citrate is converted to potassium bicarbonate chiefly after absorption and combustion. Certain side actions might be expected such as the inactivation of calcium in the diet by the citrate forming a double salt with calcium, which does not liberate calcium ions. The administration of the potassium ions might also cause a change in the sodium potassium ratio. There also might be some diuretic and a slight cathartic action.

To determine whether potassium citrate might influence the gastric secretion, 20 gms. of potassium citrate were given daily with a meal to two dogs for one month. Twenty-four eight-hour experiments on the gastric secretory response to the meal were studied during this time to determine whether an acute or cumulative effect accrued. The 20 gms. of potassium citrate given daily for one month did not depress appreciably the gastric secretion except when nausea and vomiting occurred. The carbon dioxide combining power of the blood at the end of the month was 45.7 c.c. per 100 c.c. of blood.

MONOBASIC SODIUM PHOSPHATE

MacLean and Griffiths (15) showed that the introduction of sodium acid sulphate into the stomach prevents the secretion of hydrochloric acid until sufficient neutral chloride is secreted to dilute the gastric contents to 0.2% HCl or lower. Hydrochloric acid is then secreted.

We were interested in studying the effect of monobasic sodium phosphate on gastric secretion. Twenty grams were mixed with the food and given daily over a period of six weeks to one dog. Another dog was given only 15 gms. because 20 gms. caused vomiting in this dog.

The gastric secretion of the Pavlov pouch following the meals containing monobasic sodium phosphate was depressed. The monobasic sodium phosphate decreased the appetite of the dogs and interfered with the eating of meals (Table VII). No cumulative effects on the gastric secretion were observed.

SODIUM THIOSULPHATE

Intravenous injections of one gram of sodium

TABLE VI

The effect of histidine on the basal gastric secretion in a patient with duodenal ulcer and "continuous hypersecretion." (Fasting stomach contents were removed every ten minutes for two hours)

	Total Volume Output c.c. Per Hr.	Maximum Free Acid Clinical Units	Maximum Total Acid Clinical Units	Total Acid Output mgms. Per Hr.
Average of 3 experiments on 3 successive days before histidine	224	52	64	48
Average of experiments on 3 successive days after 30 injections of histidine	464	32	52	66

TABLE VII

The effect of administration of monobasic sodium phosphate on gastric secretion in the Pavlov pouch dog

	Total Volume Output c.c.	Maximum Free Acid Clinical Units	Maximum Total Acidity Clinical Units	Total Acid Output mgms.
Administration of 15 gm. to dog No. 1				
Average of 13 control experiments	34	94	122	131
After administration of 15 gm. monobasic sodium phosphate daily for six weeks	31	65	106	104
Administration of 20 gm. to dog No. 2				
Average of 7 control experiments	74	123	142	313
After 20 gm. monobasic sodium phosphate	44	108	125	175

thiosulphate in 15 c.c. solution ten minutes after a meal produced no effect on the gastric secretion of Pavlov pouches.

DYES

The excretion of parenterally administered dyes into the stomach has been considered to be closely associated with the secretion of hydrochloric acid (16). We attempted to find a dosage of various dyes that might on intravenous administration stop the secretion of hydrochloric acid by the stomach. The dyes used were Toluidin Blue (25 c.c. of a 1% solution), Methylene Blue (25 c.c. of a 1% solution), Congo Red (50 c.c. of a 1% solution), Eosin (50 c.c. of a 1% solution), and Indigo Carmine in saturated solution. All but the last named dye are excreted into the Pavlov pouch after intravenous injection. No dosage could be found to stop the secretion of hydrochloric acid by the stomach unless a toxic dose were given. Intravenous injection of 10 c.c. saturated solution of Toluidine Blue produced no change in the secretory response of the Pavlov pouch of dogs but 15 c.c. caused death of one dog.

LOCAL IRRITANTS

Silver nitrate because of its astringent, caustic and antiseptic effect has long been used in lavaging the stomachs of patients with gastritis or peptic ulcer. Kaufmann (17) used silver nitrate for lavaging the stomach in patients with the so-called hyperacidity syndrome. He and Baibakoff (18) both stated that although the symptoms were relieved, the application of silver nitrate did not necessarily reduce the secretion of gastric juice. Although a lowering of the acidity occasionally was observed, such lowering was not the rule, and in some there was a higher degree of acidity after treatment even though the symptoms had been removed. He explained the beneficial results on the basis of finding an insufficiency of mucus before

treatment and an increase afterwards. Pavlov (19) demonstrated on dogs with a stomach pouch that 10% silver nitrate solution provoked the secretion of mucus in very large and at times enormous quantities.

Sollman (20) states that silver is not absorbed in sufficient quantity from the alimentary canal to produce systemic actions and that pills of ten to twenty milligrams of silver nitrate (made with kaolin and petrolatum) are sometimes used in gastric ulcer. As a gastric douche a solution of one-twentieth to one-tenth per cent silver nitrate followed by saline is given.

We desired to determine whether the beneficial effects reputed to have been obtained were due to change in gastric secretion. The gastric secretory response to a meal was studied before and after washing a Pavlov pouch with one: one-thousandth silver nitrate solution at two or three day intervals for one month (Table VIII). Frequent gastric lavage lowered the gastric acidity. It also increased the amount of mucus secreted, but we did not attempt to produce achlorhydria.

SODIUM SELENITE

We next attempted to produce experimental gastritis in a dog with sodium selenite, thinking that an anacidity might be produced without causing toxic symptoms. A dog's stomach was lavaged two or three times a week for six months with 50 c.c. 1% sodium selenite solution which was followed by lavage with water. Vomiting usually occurred after the lavage. Watery bowel movements occasionally occurred after vomiting, and frequently were positive for blood while the dog was on a meat-free diet. The amount of mucus in the gastric contents increased, and the secretory response to a meal and to histamine was markedly decreased, both in volume and in acidity, but achlorhydria was not produced. There was a garlic-like odor

TABLE VIII

The effect of silver nitrate lavage on the secretory response of the Pavlov pouch to a meal

	Total Volume Output c.c.	Maximum Free Acid Clinical Units	Maximum Total Acidity Clinical Units	Total Acid Output mgms.
Average of 5 control experiments in dog No. 1	27.2	56	103	80.3
After frequent lavage for 1 month	14.8	46	78	31
Average of 5 control experiments in dog No. 2	26	124.5	140	125
After frequent lavage for 1 month	15	89	99	46

TABLE IX

The effect of sodium selenite lavage (6 months) on the gastric secretory response to histamine and a meal in the dog with an intact stomach

	Total Volume Output c.c.	Maximum Free Acid Chlcal Units	Maximum Total Acid Chlcal Units	Total Acid Output mgms.
Histamine				
Average of 16 control experiments for a 2 hour period	84	120	138	320
Average of 12 experiments after lavage	12	30	52	28
Meal, fractional analysis				
Average of 6 control experiments with test meal over a 6 hour period	106	142		
Average of 20 experiments during a 6 month period of lavage	5	18		

of the breath. The red blood count, white blood count, hemoglobin and weight of the dog did not change (Table IX).

Another dog was given daily intravenous injections of 2 c.c. of a five-tenths per cent solution of sodium selenite as a control to determine whether the diminution in acidity was due to systemic or to local gastric effects. There was no reduction in the gastric secretory response of the stomach after one month of injections, and vomiting did not occur with this dosage. Vomiting did occur after intravenous injection of 4 e.c. of a one per cent solution, and vomiting occasionally occurred after 2 e.c. of a one per cent solution.

COBALT ACETATE

Twenty-five e.c. of cobalt acetate in six hundred c.c. of soya bean oil was administered by stomach tube daily for three and one-half months to two Pavlov

pouch dogs. Fifty-five experiments were performed on each dog during the administration of cobalt acetate, and thirty-one control determinations were made before cobalt administration. The secretory response to histamine was not appreciably influenced by the administration of cobalt acetate.

CONCLUSION

In the attempt to find a method of producing experimental achlorhydria, we studied the effects of a large variety of substances on the gastric secretion of man and dog. Although a diminution of acid secretion has been produced in some instances, no method that is practical for clinical use has yet been found.

We wish to express our appreciation to Miss Vivian Bass for her technical assistance.

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The Role of Protein in the Prevention of Experimental Gastric Ulcers*

By

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IN previous communications (1, 2) from this laboratory a simple method of producing gastric lesions in the albino rat was described. It was shown in these experiments that pepsin in hydrochloric acid was far more effective than the acid alone in causing these lesions. The importance of pepsin has also been stressed by other investigators in recent years although in the past the hydrochloric acid received most of the experimental attention. Howes, Flood and Mullins (3) reported that operatively produced gastric defects in cats showed a greater delay in healing in the group receiving pepsin with acid, than those receiving acid alone. Clinical observations of Vanzant,

action has been summarized by Mann (6). He discusses the use of 1—dietary correction, 2—alkalinizing salts, 3—drugs, 4—emollients.

The present authors in their past investigations have emphasized that the continuous use of Bills' stock diet (8) for rats will prevent the onset of the lesions reported. A fasting period in addition to pepsin and hydrochloric acid was necessary for the experimental production of such damage to the stomach walls. It seemed desirable to carry these investigations further so as to establish that component of the diet which is responsible for this preventive action upon continued feeding. These investigations were carried out by ob-

TABLE I

All animals were fed Bills' stock diet with added fresh vegetables on the 1, 4, 7, 10, 13 and 16th days plus a continuous supply of 2% pepsin in 0.3% hydrochloric acid solution.	No. of rats	Added factor on fasting days (2, 3, 5, 6, 8, 9, 11, 12, 14 and 15th days)	Percentage weight loss	Incidence of lesions	Group incidence of lesions
	I. Control Group.				
	55	None.	—12%	55%	55%
	II. Protein Group.				
	10	Casein.	—26%	10%	10%
	25	Gelatin	—34%	11%	
	4	Elastin.	Not estimated.	0%	
	4	Lean meat.	Not estimated.	0%	
	III. Carbohydrate Group.				
	24	Corn starch.	—20%	75%	70%
	10	Beta lactose.	—20%	60%	
	IV. Fat Group.				
	25	Butter.	—2%	88%	73%
	10	Lard.	—10%	50%	

Osterberg Alvarez and Rivers (4), confirmed by Mullins and Flood (5) seem to indicate that peptic ulcer in man is frequently accompanied by an increase of pepsin in the gastric juice.

The importance of the presence and composition of the acid gastric chyme in the formation of gastric ulcer has been stressed by a number of investigators. However, a more specific evaluation of the effect of the various components has been missing in these studies. The methods of preventing such corrosive

feeding the effect of feeding proteins, carbohydrates and fats to various groups of rats during the fasting period. This seemed of particular interest since the nutritional factor has been stressed by other investigators (7).

EXPERIMENTAL

The general plan of these investigations was to supply various factors on the fasting days. A total of 168 albino rats averaging three months in age were fasted two days and fed the Steenbock-Bills' stock diet (8) with added fresh lettuce or sliced carrots on the

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third day, in recurrent cycles, for a period of sixteen days. A 2% solution of pepsin prepared daily, (1:10,000 granular pepsin, Parke, Davis and Co.) in 0.3% hydrochloric acid was supplied to all the rats ad lib by means of stoppered flasks with glass tube outlets.

The above animals were divided into 4 groups as shown in Table I. The control group consisting of 55 animals received no dietary factor on the fasting days. The remaining 3 groups of 113 rats received a dietary factor on the so-called fasting days. The protein group (44 rats) received either casein, gelatin, elastin, or lean meats; the carbohydrate group (34 rats) either corn starch or beta lactose; the fat group (35 rats) butter or lard. These dietary factors were supplied ad lib. The average consumption per rat was about 5 grams daily.

The results are summarized in Table I. The lesions at autopsy were generally found to be multiple, with rounded margins and umbilicated centers. The gross and microscopic appearance of submucosal edema, cellular infiltration with varying degrees of desquamation and mucous membrane erosion were similar to that previously seen and described (1, 2, 9).

DISCUSSION

It is evident from the results of these experiments that proteins have a far greater protective power against the development of gastric lesions in the rat than either carbohydrates or fats. The incidence of lesions in the protein group was 10% in comparison with an incidence of 70% in the carbohydrate and 73% in the fat groups. Moreover the severity and the number of these lesions were small in the protein group in contrast to the carbohydrate and fat groups.

The mechanism of the protection afforded by the proteins is still problematic. There are in the main two general theories that may be presented. 1. Proteins supply a nutritional factor which increases the resistance of the stomach walls against the combined attack of pepsin and hydrochloric acid. 2. The digestive power of the pepsin is interfered with. The latter may be due to the "competitive retardation" of the products of peptic digestion of proteins or it may be caused by the acid combining properties of proteins.

The production of gastric ulcers on diets which were deficient in proteins were reported by several groups of workers. Pappenheimer and Larrimore (10) demonstrated that the gastric lesions in the rat were related to a deficiency in the diet. Hoelzel and Da Costa (11) produced gastric lesions in rats on low protein diets and found that alternate days of fasting increased the severity and the number of the lesions. They suggested a protein deficiency as a possible cause for these lesions. Wceh and Paige (12), while studying nutritional edema in dogs, found true peptic ulcers in a large percentage of their dogs maintained on a low protein diet. Howes and Vivier (13) produced gastric lesions in rats kept on a diet deficient in vitamins and proteins. These lesions were prevented by the feeding of yeast which is rich in proteins and the vitamin B complexes.

One of the explanations for the above behavior of low protein diets may be found in the amino acid deficiency theory of Weiss and Aaron (14). According to this hypothesis an insufficiency of certain essential amino acids would reduce the resistance of the tissues to a corrosive agent. These authors have cited, for

experimental evidence, the prevention of the gastric ulcers, following the Mann-Williamson operation in dogs, by the injection of histidine hydrochloride. However, this beneficial effect could not be confirmed by Sandweiss, Salzstein and Glazer (15) in their recent investigations. Moreover the senior authors of this paper (9) in their experiments found no preventive effects of histidine injections upon the production of gastric lesions in the rat. Thus the experimental support of the amino acid deficiency hypothesis is not sufficient at present. All of the experiments with protein deficient diets can be equally well explained by postulation of a positive inhibitory effect of the protein in the diet upon the activity of pepsin.

It is well known that the activity of certain enzymes may be stopped even when all other conditions are favorable, by the accumulation of the products of the reaction; and in certain circumstances, the action of the enzyme may be reversed so as to accelerate a change in the opposite direction to that in which it ordinarily acts. Wasteneys and Borsook (16) have carried out a very extended and systematic investigation of the reversion of peptic digestion. Thus proteins may very well prevent the further action of pepsin as they are digested due to the "competitive retardation" of the digestion products. Such an explanation may be offered for the inhibitory action of gastric mucin, chondroitin sulfuric acid and mucosin sulfuric acid (17, 18, 19, 20) as all of these can be isolated from the intermediary stages of protein hydrolysis.

Proteins may also inactivate pepsin in a different fashion. Due to the acid binding property of proteins a change in the pH of the medium can take place to such a degree that the optimum conditions for pepsin activity no longer exist. Thus 1 gram of gelatin or casein can combine with approximately 8.0 to 9.0 c.c. of 0.1 normal hydrochloric acid (21). The rats in our experiments have consumed an average of 5 grams of protein daily on the fasting days and they drink an average of about 8 c.c. of 0.1 normal hydrochloric acid daily (contained in the pepsin hydrochloric acid mixture). The pH of such a mixture would be about 3.8 to 4.0 in a test tube with gelatin as a protein. Since the optimum pH of pepsin is about 1.8 to 2.2 (depending upon the nature and the concentration of the substrate) such a change of hydrogen ion concentration will reduce the activity of pepsin to a small fraction of its optimal activity. Thus proteins can inactivate pepsin by their acid binding property.

While conceivable, it is unlikely that a nutritional deficiency of proteins played a part in the production of gastric ulcers in these experiments. This conclusion is based upon previous experiments (1, 2) where it was shown that animals maintained on Bills' stock diet with fasting and feeding cycles alone developed no lesions. On the other hand a second group on a similar regime but receiving pepsin in hydrochloric acid instead of water showed a 96% incidence of gastric lesions.

Weight loss seemed to play no part in the formation of the lesions. In the gelatin group, where the weight loss was the highest (—34%) the incidence of lesions was the lowest. In the butter group where the weight loss was the least (—2%), the incidence of lesions was 88%, and higher than in the control group. The high incidence in the butter group was also associated with

severe and more numerous lesions. Likewise in the experiments of Howes and Vivier (13), weight loss alone did not account for formation of lesions in their rats.

Thus the evidence is more in favor of protein acting as an inhibitory agent to the activity of pepsin. This may take place by either one or both of the inhibitory mechanisms previously discussed.

Whether this protective mechanism of proteins will be of value in the prevention and treatment of peptic ulcer in man will require careful clinical investigation.

It is hoped that the investigations which are in progress at present will elucidate more exactly the

mechanism by which proteins inhibit the formation of gastric lesions.

SUMMARY AND CONCLUSIONS

1. The relative importance of proteins, carbohydrates and fats in the prevention of ulcerative gastric lesions was investigated.

2. Proteins in the form of casein, gelatin, elastin and lean meat afforded a marked degree of prevention in contrast to the carbohydrate and fat groups.

3. The mechanism of this protection is ascribed to the interference of proteins with proteolytic activity of pepsin, which may be due to a "competitive retardation" of digestion products or the acid combining power of proteins or the combined effect of both actions.

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Clinical Notes on the Use of Color Filters in Sigmoidoscopy

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THE purpose underlying the use of color filters in sigmoidoscopy is to render with greater clarity and detail structures otherwise scarcely visible to the eye. The principle involved is one commonly utilized in photomicrographic work in which a filter containing the complementary or contrasting color is interposed between the source of illumination and camera in order to give more "blackness" or contrast to structures which we wish to register on the photographic plate.

In sigmoidoscopic work we have found the green (type X, Wratten) and red (type A, No. 25, Wratten) most useful. Most of the pathological conditions encountered in sigmoidoscopy fall in the red range and are viewed with the green filter. Although the true complementary color is blue the filter is too dense for visibility. The green filter contains blue and transmits sufficient light from the sigmoidoscopic bulb. With the aid of the green filter punctate follicular lymphoid hyperplasia under the normal pink or inflamed

mucosa stands out clearly. The characteristic three stage pathology of acute bacillary dysentery (i.e. 1—punctate follicular hyperplasia; 2—punctate follicular necrosis; 3—discrete and confluent ulceration) can be followed with ease. The finer ramifications of the mesenteric arteries can be studied and will reveal a

Table showing applicability of the green and red filters in sigmoidoscopy

Green Filter:	Red Filter:
Arterial and periarterial lesions.	Hemorrhoidal veins and variceties.
Embolie lesions	Depth and character of ulcer edge.
Tumors.	Bluish pigmentation.
Lymphoid hyperplasia under inflamed mucosa.	
Outline and floor of ulcer.	

characteristic tortuosity in arteriosclerosis comparable with that seen in the retinal vessels of the same individual. With the aid of intermittent intestinal suction through the inflation tube of the sigmoidoscope their degree of patency and elasticity can be demonstrated. Embolic lesions in the smaller vessels are more common than thrombosis of a large mesenteric vessel in subacute bacterial endocarditis. The green filter makes the lesion stand out as a characteristic petechia with pale center. For the unpractised eye the sigmoidoscopic telescope will be found useful. Purpuric eruptions in purpura hemorrhagica, leukemia and agranulocytosis are visualized with greater clarity; also the outlines and floors of ulcers and smaller tumors such as the sessile adenomatous polyps, adenoma malignum, adenoma destruens or leiomyoma.

The red filter is used to study bluish to slate colored

pigmentation of the mucosa, hemorrhoidal veins and the depth and character of ulcer edges. In plumbism we have been able to demonstrate in three cases the presence of lead sulphide particles along the mesenteric arteries as well as a more diffuse bluish stippling of the intervening mucosa.

The practical application of these filters can be shown in a simple way by using colored sigmoidoscopic view plates such as are seen in Bensaud's or similar text book. During sigmoidoscopy we hold the filter between the light source and the eye. Since the filters are obtainable as colored gelatin sheets they may be fitted into the window of the sigmoidoscope or as two separate discs which may be swung in place as needed. It is preferable to obtain the gelatin strips cemented between two pieces of optical glass as specified above.

Continuous Drop Feeding for the Treatment of Ulcers of Stomach and Duodenum

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THE treatment of ulcers of the stomach and the duodenum must be based on the same principles which have been found successful in the treatment of ulcers of any other organ, with due consideration to the peculiar structure and function of the stomach and of the duodenum. Rest and prevention of irritation are the fundamental principles on which must be based and are actually based all successful treatments of ulcers, with the possible addition of disinfection, improvement of circulation, special medications, surgical procedures alone or combined.

The peculiar structure and function of the stomach and of the duodenum make it physically impossible to apply any of these means 100% efficaciously. In fact even if theoretically we should attempt to act as we do with limbs, that is abolish their function in order to obtain a perfect rest by casts, slings, special positions, etc., and consequently withdraw all solid or fluid foodstuff and beverages with the intention of putting the stomach and duodenum at rest, we know that rest would not be achieved. We all know more: the complete withdrawal of food and beverages would cause perhaps more activity of the stomach and of the duodenum and the ulcerated area would become more irritated by the undiluted acid secretions of the stomach.

Theoretically in order to achieve rest and prevent irritation we should completely withdraw beverages and food and at the same time stop the acid secretions of the stomach. Evidently we cannot do so. I shall not dwell on the limited efficiency of disinfectants, special medications, attempts to improve the circulation of the ulcerated area, etc.: consequently any form of treatment must be a compromise, the best being the best compromise. The treatment advocated in this

paper seems to be a practically successful compromise and conforms to our present knowledge of the digestive processes and of scientific therapeutics.

It is assumed that neither peristalsis nor acid secretions can be completely prevented: it is also assumed that disinfectants, special medications, means of improving the circulation around the ulcerated area or any other supposedly direct means of influencing the healing of the ulcer have proven rather disappointing. Consequently, the best compromise appears to be a method of proper feeding of the patient which will increase his stamina and resistance while reducing peristalsis, acid secretions, direct or indirect irritation and infection of the ulcerated area to a minimum. These desiderata seem to be realized by the following method: The patient is fed by the drop method day and night through a small rubber tube introduced through the wider nostril into the esophagus *not beyond the cardia*.

In this method three points are of fundamental importance: 1. The continuous day and night feeding by the drop method: 2. The special nutrient medium: 3. The position of the tube which should never be pushed beyond the cardia.

The continuous drop feeding prevents accumulation of the nutrient medium in the stomach, reduces acid secretions to the minimum and keeps them diluted to the maximum and affords complete feeding. The nutrient medium is based on milk, white of eggs mixed with water and gum acacia to which fruit juices and or special medications according to cases and indications may be added: the important point about the nutrient media is that they should supply the fluid, the calories and the vitamins required by each patient and be non irritant to the gastro-duodenal mucosa. The rubber tube should never be pushed beyond the cardia, because its presence in the stomach or duo-

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denum constitutes a constant irritation of the whole organ and may irritate directly the ulcerated area. I insist on this point, because no matter how soft the rubber tube may be at best it must tickle the gastric or and duodenal mucosa, when it does not cause true irritation or direct pressure on some point. All living tissues will react to the presence of foreign bodies, the gastro-intestinal tract being no exception to this rule, reacts by increased peristalsis and secretion. The esophagus seems not to react to the presence of this small soft rubber tube practically hanging in its middle and hardly touching its walls.

The continuous day and night drop feeding method has been used for many years as the almost ideal feeding method for patients who had to be operated on the stomach, duodenum and occasionally on the biliary tract. Being a surgeon practically only advanced chronic cases are referred to me and for this reason my experience in the treatment of early ulcers of the stomach and duodenum has been limited. However, lately many colleagues have referred to me cases for diagnosis with my special X-ray apparatus and thus I had the opportunity to observe several early cases in close succession and treat them with very encouraging results.

The matter of the nutrient media requires still a great deal of consideration and study. In one case of bleeding ulcer, strong tea and milk were very effectual

in stopping the bleeding while supplying sufficient fluid and nourishment. The matter of medication requires also a great deal of consideration: atropine to reduce spasticity, morphine, pantopan, etc., to allow restful sleep or reduce excessive nervousness: strychnin, arseniate of iron, blood transfusion, complete rest in bed to bolster up a rundown organism have been used in connection with the continuous day and night drop feeding method. When to stop the drop feeding and resume normal feeding may be determined by X-rays and the general condition. The average amount of fluid nutrient medium has been 3,000 c.c. every twenty-four hours: it may be increased or decreased according to cases bearing in mind that it is absolutely indispensable to prevent accumulation of fluid in the stomach.

Although all the phases of this method of treatment have not been thoroughly studied due to the limited number of cases treated the results have been so encouraging as to induce me to present it to the medical colleagues in the hope of obtaining their cooperation in making it as efficacious as possible.

In connection with this subject I am happy to mention and give due credit to the pioneer works of Dr. Max Einhorn on duodenal feeding; the contribution of Dr. Rowland on intragastric drip, and Dr. Asher Winkelstein on continuous alkalized milk drip into stomach for therapy of peptic ulcer.

The Follicular Lesions of Vitamine A and C Deficiencies: A Critical Survey

By

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THE cutaneous manifestations observed in various forms of avitaminosis have received considerable attention in recent years. Especially is this true of the primary follicular lesions encountered in vitamine A deficiency, where they occur as part of a generalized epithelial keratinizing process (Frazier and Hu (1), Loewenthal (2) and others). The pilo-sebaceous apparatus may, however, also be affected in scurvy, such alterations being less intense and apparently secondary in nature. In a previous publication (Scheer and Keil (3)) two instances of scurvy in adults were recorded for the purpose of providing data on skin lesions of this sort. In one example, the follicular papules were somewhat similar to those seen in vitamine A deficiency: it was, however, noted that the patient had adopted a much restricted dietary regimen for several years and that, as a consequence, the possibility of simultaneous lack of the fat-soluble factor could not be eliminated entirely. This view seemed reasonable, considering the frequent occurrence of multiple vitamine deprivations, though the ordinary substantiating evidence, such as night blindness (hemeralopia) was lacking. In the second case, however, the superimposition of a hemorrhagic component provided a fundamental feature differentiating the follicular lesions of scurvy from those of vitamine A deficiency. In further support of this thesis, there

will be cited two additional cases of scurvy in which characteristic perifollicular petechiae were encountered as well as several other phenomena worthy of description. In concluding the paper an attempt will be made to set forth evidence indicating the essential differences between these two types of follicular eruptions, the recognition of which may aid in the detection of early cases of avitaminosis or hypovitaminosis.

Case 1. The patient was a woman, aged 29, who was observed for a period of about 6 weeks during the latter part of 1934. About 16 months before observation she complained of moderately severe diarrhea, characterized by the passage of from 3 to 5 stools daily; these contained mucus but no blood. She was placed on a diet consisting of egg-nogs, malted milk, toast, chicken soup, and small amounts of butter and orange juice. Vegetables, fruit, meat, and fish were excluded. On this regimen the diarrhea improved temporarily. About 4 months later there was an exacerbation of this complaint, as a result of which the dietary restrictions were enforced more rigorously. Shortly after, the fear of precipitating another attack of diarrhea caused the patient to restrict the intake of foods even more; orange juice was discontinued and she now subsisted largely on cereals, soups, and some boiled milk. A mild recurrence of the complaint led her to seek hospitalization; on this occasion proctoscopic examination revealed several ulcerations in the rectum and a barium enema showed incompetence of the ileo-caecal valve with spasticity and loss of haustrations in the colon.

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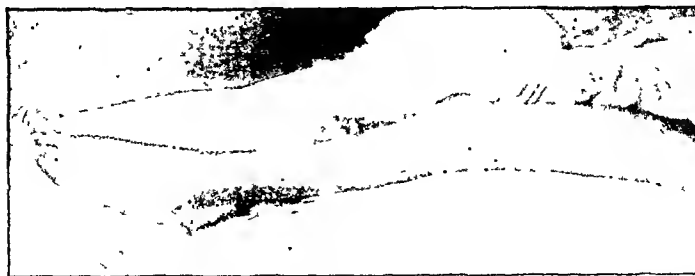


Fig. 1. Perifollicular petechial eruption of scurvy; each hair follicle shows a central cornified mass of moderate extent, with delicate deformed hairs, surrounded by a tiny zone of hemorrhage. Photograph taken several days after institution of vitamine C therapy when the hemorrhages were beginning to resorb.

Although no special efforts were made to treat the condition, the diarrhea ceased spontaneously and she was discharged as a case of ulcerative colitis. Several months later she began to complain of weakness and debility, the symptoms being aggravated by an upper respiratory infection of several weeks' duration. About two months before observation she experienced pains in the bones and joints, followed within a short time by the occurrence of tender gums that bled on the slightest trauma. The patient also noticed the appearance of small lumps in the skin, particularly on the lower extremities, the lesions rapidly assuming a hemorrhagic aspect. At about this time, larger black and blue spots were noted on the thighs. The left ankle became swollen and painful, the skin overlying the affected articulation showing a deep purplish discoloration. She complained of moderate cough. Three days before observation the patient felt feverish; the temperature rose sharply to 103° F. During the entire illness she had lost about 50 pounds in weight. There was no history of night-blindness.

On physical examination the patient appeared pale and emaciated. She was dyspneic, and she coughed. The teeth were covered with sordes. The alveolar margin of the gums, on the internal as well as the external aspect, was bright red, spongy, and bled easily. The edentulous spaces were apparently spared. The tonsillar remnants were ecchymotic. There was general dryness of the skin. In addition, the skin of the abdomen, arms, and lower extremities revealed definite hyperkeratosis of the hair follicles, with numerous delicate deformed curly hairs; there were occasional areas where the hairs were wanting. On the lower extremities where the eruption was characteristic, each lesion was surrounded by a zone of erythema or frank hemorrhage, according as the petechia was in the process of formation or in the stage of advanced development (Fig. 1). Here also, there were numerous delicate deformed hairs, many of which were curled up on themselves. There was evidence of old ecchymoses about the thighs, calves, and along the tibias. A large fresh ecchymosis with marked edema of the area was noted about the region of the left tendo achilles. There were physical signs of a pneumonic process in the left chest and, probably also, of atelectasis of the lower lobe of the left lung.

The hemoglobin was 38 per cent; the red cell count 2,810,000. The white cell count was 5800 with 71 per cent polymorphonuclear leucocytes. The tourniquet test was markedly positive, causing a fine spray of numerous hemorrhagic puncta in the fold of the elbow. The bleeding time, coagulation time, and platelet count were normal. The temperature ranged between 103.8° F. and 104.4° F. Because of the marked anemia, she received a blood transfusion. Orange juice (500 c.c.) was given immediately and, by the following morning, the general condition of

the patient was eminently improved, contrasting with the precarious state on initial observation. Within 24 hours the gums were less red and spongy. During the succeeding nine days crystalline cevitamic acid, 3 grains daily, was administered by mouth; tomato juice, orange and other fruit juices were eliminated from the diet. Improvement continued unabated and, within the next few days, the condition of the gums improved considerably and the skin lesions (ecchymoses and perifollicular petechiae) began to undergo rapid involution. Within a period of from one week to 10 days, the texture of the skin became almost normal, although the faint brownish spots marking the situation of the perifollicular hemorrhages, required about a month for complete disappearance. The patient gained weight steadily and the abnormal physical signs in the left lung cleared up completely, with the exception of slight dullness at the base, attributed to the presence of thickened pleura. The tourniquet test became negative about 10 days after the institution of vitamin C therapy.

Comment: From the clinical point of view the case was a typical one of scurvy, apparently uncomplicated by any other vitamine deficiency. There were no symptoms referable to deprivation of fat-soluble factor, such as night-blindness. The association of broad areas of ecchymoses, spongy bleeding gums, and perifollicular petechiae constitutes a triad of signs commonly observed in adult scurvy. The immediate response to orange juice and the unabated improvement under cevitamic acid was striking, contrasting with the slower course seen in patients recovering from vitamine A deficiency; this point will be elaborated upon in a subsequent section. The general dryness of the skin was probably caused, for the most part, by loss of fluid through diarrhea, aided perhaps by fever; this sign was not noted in the next case in which gastro-intestinal symptoms were lacking.

Case 2. This patient was a woman, aged 44, who complained of pain about the ankles and swollen bleeding gums of 6 months' duration. About 18 years before the present observation she had an operation for ectopic pregnancy. Shortly after, she experienced nausea and epigastric distress, causing her to limit intake of foods to such a degree that, during the past 10 years, she had subsisted almost entirely on cereals, eggs, bread and coffee. Fresh vegetables and fruits were completely eliminated from the dietary regimen; indeed, the distaste for fruits became so intense that the mere sight of them caused distress. Eight months before observation she learned that she had high blood pressure, for the alleviation of which eggs were eliminated. In the past few weeks the diet had, therefore, consisted of but cereals, coffee, and cream, and bread. About six months before that, the gums became

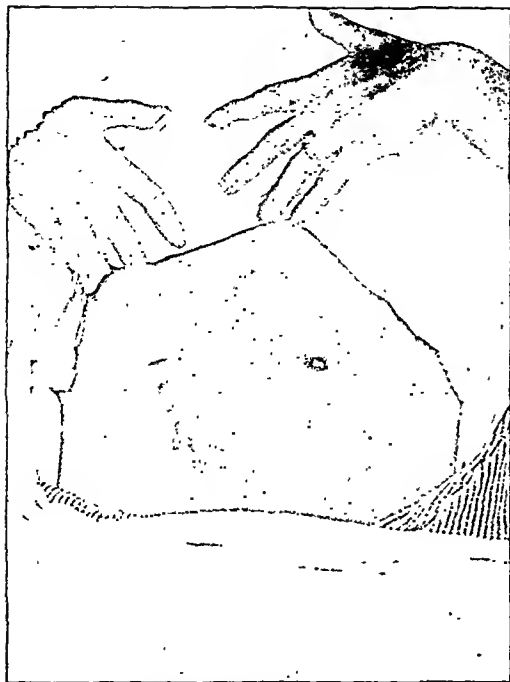


Fig. 2. Scorbutic hemorrhage into the inferior angle of a scar on the abdomen; slight hemorrhage also in the upper angle.

swollen, tender to touch, and bled on the slightest trauma. At the same time she noted pains in the lower portions of the tibiae and about the ankles, the skin overlying these parts becoming swollen and ecchymotic.

Physical examination showed a thin, poorly nourished woman whose skin was not particularly dry. The gums were turgid, colored purplish red, friable, spongy, and bled easily. There was a large ecchymotic area about the left ankle. Over both legs and over the lower portions of the thighs, there were pinhead perifollicular petechiae characteristic of those encountered in scurvy. As in the first case, the centers showed moderate degree of hyperkeratosis, with many scattered curled delicate hairs arising in each follicle. Similar lesions were seen on the lower part of the back. A remarkable feature was the presence of a large area of hemorrhage situated mainly in the inferior angle of an operative scar located on the abdomen (Fig. 2). The tibiae and ankles were tender and mobility was limited owing to pain.

The hemoglobin was 72 per cent; the red blood cell count 4,100,000. The platelets numbered 250,000. The tourniquet test was markedly positive; the bleeding time, coagulation time, and clot retraction were normal. Examination of urine specimens revealed no abnormal findings. There was no evidence of bleeding from the gastro-intestinal tract (gastric contents and specimens of stool). Roentgenologic examination of the chest (heart and lungs) disclosed no abnormalities; in addition, there was no evidence of subperiosteal elevation of the bones of the lower extremities. Despite the previous dietary restrictions, there was no diminution in blood protein (6.6 mgs. per cent). The blood pressure was 180 systolic, 100 diastolic.

The patient was given liberal quantities of orange juice and a soft diet rich in vitamins. The improvement was dramatic; the swollen gums diminished in size and turgor, bleeding ceased, and the tenderness disappeared; the

ecchymoses and follicular hemorrhages underwent rapid involution, the original sites of the latter lesions being marked by the presence of tiny pigmented spots centered by a hair in most instances; the tourniquet test now became negative. The appetite improved and she no longer experienced the feeling of distaste for raw fruits and vegetables.

Comment: The perifollicular petechiae encountered in this case were the precise counterpart of those seen in the first patient. The clinical course and response to ingestion of orange juice were also identical. A remarkable feature was the presence of an area of hemorrhage in a scar situated on the abdomen, and it is probable that the bleeding was subcutaneous in type with infiltration of the upper layers of skin. As in the first case there was no clinical evidence pointing towards deprivation of the fat-soluble factor; in addition, the diet, though markedly restricted, had contained cream which is an excellent source of vitamine A.

FOLLICULAR LESIONS OF SCURVY

(a) *Introductory General Remarks:* The pilo-sebaceous apparatus is a structure supplied by a rich plexus of capillaries. It appears that this system is not established in its definitive form until the age of 4 or 5 years, only to be influenced profoundly at puberty (Frazier and Hu (1b)). It is probable that nutrition of this structure is accomplished through the blood and lymph channels (tissue spaces), although present knowledge of the precise mechanism is fragmentary. Disease of the hair follicles may be a primary process when the epithelium is initially involved or the changes may be secondary in nature when, for example, there is a defective blood supply or interference with that portion of the circulation. In many instances this distinction cannot be clearly established. In the case of vitamine C deficiency, there is evidence that disturbances in the blood vessels constitute the primary causative factor and that hyperkeratosis of the hair follicles and other changes (curling, thinning, and temporary loss of hair) are of secondary origin. It has been shown (Aschoff and Koch (4), Wolbach and Howe (5)) that the fundamental defect in scurvy appears to be the inability of the supporting tissues "to produce and maintain intercellular substance." By implication based on thorough general pathologic studies, Aschoff and Koch suggested that the hemorrhagic manifestations of vitamine C deficiency are caused by an impairment of the intercellular substance supporting the blood vessels. According to this view, then, the endothelium of capillaries is unable to form the normal cement substance allowing for diapedesis of red blood cells and serum.

The distinguishing feature of the eruption seen in scurvy is the occurrence of tiny hemorrhages around the hair follicles, producing perifollicular petechiae. So far as the superficial vessels of the skin are concerned, maximal capillary fragility seems to be confined, for the most part, to the blood channels supplying the pilo-sebaceous apparatus. In some cases this can be shown experimentally in humans by means of the tourniquet test (Korbsch (6)). In one instance, for example, the application of a tourniquet about the right arm produced numerous tiny hemorrhages confined principally to the areas about the hair follicles on the forearm (Scheer and Keil (3)). In other

patients, however, this procedure gives rise to innumerable hemorrhagic puncta, apparently independent of the follicular openings; it may be agreed, therefore, that other vessels of the superficial skin may apparently also be affected.

Perifollicular hemorrhages are likely to be more intense and to be encountered with greater frequency in areas of the body where the pilo-sebaceous apparatus is more highly developed and in races where the hairy system is more pronounced (Salle and Rosenberg (7)); indeed, unusual variations in situation of these patches may frequently be correlated with abnormal distribution of hair. There may, however, be occasional exceptions to these rules. It is probable that these factors likewise influence distribution and intensity of the process seen in the follicular eruption of vitamine A deficiency.

The clinical phenomena of scurvy (bleeding gums, massive hemorrhages about the muscles and subcutaneous tissues, the hemorrhagic phenomena produced in the more superficial areas of skin, the positive tourniquet test, etc.) constitute evidence of the predominant part played by vascular disturbances in the symptomatology. When the missing vitamine is replaced in the diet, these manifestations disappear rapidly as a rule.

(b) *Clinical Features of the Skin Lesions:* In its well-established form the perifollicular petechial eruption appears to be pathognomonic of scurvy. As far back as 1871, Lasèque and Legroux (8) recognized its diagnostic importance as an early sign of the disease. Of 75 cases of the condition seen by Salle and Rosenberg (7) in 1917, 10 showed this manifestation as the presenting sign. During the World War when the opportunities to study the disease on an extensive scale were ample, numerous observers stressed the clinical significance of these skin lesions (Feig (9), Pfeiffer (10), Arneth (11), Wiltshire (12) and Korbach (6) among others). Of the 4 cases of this disease observed by me in civilians, 3 of them presented the dermatosis in its typical morphology. In the remaining instance it was differentiated with difficulty from the somewhat similar eruption of vitamine A deficiency, and the view was therefore expressed that the initial follicular lesions of scurvy may sometimes clinically resemble those seen in patients suffering from deprivation of the fat-soluble factor. This difficulty, however, arises only in occasional instances, as will be shown in a consideration of the fundamental attributes of both eruptions. In two cases of scurvy in infants the follicular hemorrhagic dermatosis was not encountered; this manifestation is but rarely mentioned in pediatric texts and monographs. The characteristic skin lesions are, therefore, met with most frequently after the age of puberty.

The eruption manifests particular favor for the extensor aspects of the lower extremities (legs, anterior and inner parts of thighs) and of the upper limbs (forearms, occasionally the arms). It is also seen on the lower part of the abdomen, and occasionally in advanced cases, on the chest. Hair-free portions of the body and areas with a poorly developed pilar system usually remain unaffected (popliteal spaces and elbows) (Salle and Rosenberg). The face, scalp, hands, and feet appear to be spared. It is found in its most typical form on the legs where practically

every hair follicle may be involved by the hemorrhagic process. It is not unusual to see perifollicular petechiae at sites of predilection, whereas less favored areas, like the abdomen, may reveal simple hyperkeratosis at the mouths of follicles, with an occasional surrounding hemorrhage. In the latter situation the individual lesion may resemble that seen in vitamine A deficiency; unlike the latter condition where keratosis is usually a pronounced feature, often leading to secondary phenomena (pressure atrophy), the accumulation of hyperkeratotic masses is moderate in intensity.

When the hand is passed over the affected areas in scurvy, the impression of a nutmeg grater is produced and the older clinicians (Jessner (13)) spoke of the phenomenon as "lichen scorbuticus" or "scorbutic goose-flesh." This attribute is, however, not pathognomonic of any single skin ailment; it merely describes the sensation imparted to the palpating hand by hyperkeratotic accumulations as encountered in many cutaneous conditions (lichen pilaris, pityriasis rubra pilaris, follicular ichthyosis, follicular papules of vitamine A deficiency, etc.). In scurvy, therefore, involvement of the follicular apparatus also occurs, but it is secondary in type and less intense than in the case of vitamine A deficiency. It is less likely to cause "atrophic depressions" by pressure of hyperkeratotic masses; for example, gaping cavities are not seen when the central plugs are removed, as in the skin lesions attributed to lack of the fat-soluble factor.

The eruption of scurvy appears to have the following course. The initial disturbances in the peripilar capillaries cause nutritional alterations in the follicular apparatus, leading to hyperkeratosis as well as curling and thinning of the hair. In this early stage, and especially in certain locations (abdomen), gross hemorrhage may not be apparent clinically, although it is probable that mild degrees of interstitial extravasation of blood could be demonstrated on histologic examination. The usual onset is in the form of bright red puncta about hair follicles; these may be scattered at first, then cover an entire limb. As the lesions increase in size, they become bluish red, forming lichenoid papules owing to the central projection of hyperkeratotic material, aided in some cases by the transudation of serum. In its fully developed stage the lesions vary in size between that of a pinhead to that of a split pea in occasional instances. Subjective symptoms attributable to the dermatosis are uncommon, itching being a rare complaint. In its later course the hemorrhage is resorbed slowly, leaving pigmented spots (hemosiderin) for months. The centrally situated hairs may be broken off, at times may have fallen out. If the deficient diet is maintained, the eruption may remain in the same state for months. When adequate therapy is instituted, there takes place a dramatic restitution ad integrum, which will be described in a subsequent section.

As regards secondary infection, pustulation and scarring, observations differ relative to their incidence and significance. Arneth described large follicular petechiae, occasionally capped by central pustules which later dried without undergoing any other changes. It has been stated that furunculosis is a fairly frequent complication in such cases. Under these circumstances, scarring of some lesions may be

expected, but the phenomenon is uncommon and secondary in type. In agreement with Salle and Rosenberg, I am unable to confirm the high incidence of such secondary complications, notwithstanding the point that in several of the patients observed by me, the condition had been present for many years.

It has been stated that in the typical form described the eruption is pathognomonic of scurvy. The dermatosis is readily distinguished from the "hemorrhagic folliculitis" occasionally observed in Gaucher's disease (larger isolated lesions up to a dime in size, occurring on the inferior extremities, few in number, healing with the formation of large pigmented scars) and from a host of diseases producing skin eruptions with incidental, rare, isolated, and unimportant involvement of hair follicles as compared with the other features presented by the dermatosis (Henoch-Schönlein-Osler syndrome, uremia, acute lupus erythematosus, subacute bacterial endocarditis, varicose complex and many other affections). On the basis of the pathologic observation that both rheumatic fever and scurvy affect collagenous tissue throughout the body, it has been suggested by Rinehart (14, 15) and his co-workers that the former disease may be the result of the "combined influence of vitamin C deficiency and infection." It is not within the province of this paper to enter into a detailed discussion regarding the probability of this hypothesis, but it does seem pertinent to note that, although hemorrhagic phenomena occur in the course of rheumatic fever, they bear no clinical similarities to the lesions encountered in scurvy (Keil (16)).

(c) *Pathology*: The vascular alterations producing the typical morphologic attributes of the eruption constitute the one striking characteristic feature, the remaining changes in the epidermis appearing to be of banal type. In 1871, Laségue and Legroux, on the basis of a histologic study of these skin lesions, noted that the hemorrhagic extravasation was disposed principally about the hair follicles. In the detailed microscopic examinations practiced by Nicolau (17), swelling of the endothelial walls of the perifollicular capillaries was noted; the extravasation of red blood cells in isolated groups and in small numbers, without particular damage to surrounding tissues, was stressed by this observer who regarded this feature as evidence of diapedesis through the parietes of the affected vessels, an observation which is in essential agreement with the view relating to the inability of endothelial cells to form normal cement substance in this disease. Nicolau also found that in occasional instances there was transudation of serum in moderate amounts. In a previous paper (Scheer and Keil) there was appended a histologic report on an "erythematous" follicular papula that on gross examination showed but slight evidence of hemorrhage, although the remainder of the eruption, shortly after the initial appearance, became definitely hemorrhagic in type. Study of this relatively early lesion revealed the presence of interstitial extravasation of red blood cells, most conspicuous about the hair follicles, associated with transudation of serum which explained, for the most part, the gross elevation of the lesion. It was difficult to distinguish the outlines of the peri-

follicular capillaries owing to the swelling of the walls, about which there was a moderate infiltration of lymphocytes. That the pigment found in the tissues is derived from the blood was shown by Nicolau who obtained positive iron reactions; in advanced cases, therefore, the pigmentation is probably caused by the deposition of hemosiderin.

The epithelial changes seen in the case reported by Scheer and Keil were apparently secondary in type. The hyperkeratosis of the follicular orifices was moderate in extent, hardly rivaling the intensity of the process as seen in vitamin A deficiency. There was no resultant pressure on surrounding structures; hence, little likelihood of secondary pressure atrophy with the formation of gaping cavities on extrusion of the central keratotic material. In healing, therefore, conspicuous depressed areas marking the former sites of lesions are not to be expected, except rarely when there is superimposition of infection. The significance of the finding of hypertrophied arrectores pilorum muscle as described by Aschoff and Koch, Nicolau and others, is as yet unknown.

(d) *Therapeutic Response*: Until the advent of crystalline extracts of vitamins, it was most difficult to apply an absolute therapeutic test. For example, orange juice is said to contain not only vitamin C, but also vitamin A or its precursor carotene (Jeghers (18)) in amounts sufficient to cure rats suffering from xerophthalmia (Wolbach and Howe (19)). In a similar manner, Frazier and Hu (1a) treated their original series of cases of vitamin A deficiency by means of a balanced diet combined with cod liver oil and one lemon a day (vitamin C). There are, however, a few reports indicating that the therapy used was such as to warrant the drawing of accurate conclusions relative to the precise vitamin lack.

In the first case cited in this paper orange juice was given on the first day of observation, with striking amelioration of the symptoms. As the foodstuff also contains vitamin A or its precursor, it was interesting to note that rapid improvement continued with the oral administration of cevitic acid (crystalline vitamin C). Equally striking was the rapid involution of the perifollicular hemorrhages, practically complete resorption taking place in about 10 days, though faint brownish spots persisted for several weeks. The central keratotic plugs were extruded and towards the end of the period of observation of some 6 weeks many normal hairs seemed to be regrowing. At this time, the character of the skin could be designated as normal. The rapidity with which the skin lesions underwent involution in the cases observed by me would seem to contrast with the slower course recorded in most of the patients recovering from the effects of deprivation of vitamin A. Where the central keratotic plugs require many months for healing or leave depressed areas at the sites of hair follicles, in the absence of gross secondary infection, there may be reason to suspect coincidental lack of the fat-soluble factor, though the latter may in some cases be so slight in degree as to fail to cause obvious clinical symptoms. It is undoubtedly true that the simultaneous lack of both vitamins A and C occurs not infrequently, and it will be an interesting problem

to determine the relative part played by each in the evolution of the skin lesions observed in such instances.

Follicular Lesions in Vitamine A Deficiency:

(a) *General Concept of the Disease and General Clinical Data:* Deficiency in the fat-soluble factor gives rise to a systemic condition in which there occurs keratinizing metaplasia of the various epithelial-lined structures in the body (Wolbach and Howe (19) and others). The site of predilection are the eyes (night blindness, xerosis, Bitot's spots, pigmentation of the conjunctiva, keratomalacia) and the skin (generalized dryness, follicular lesions), but experimental evidence in animals (Wolbach and Howe, Goldblatt and Benischek (20)) and postmortem examinations in human beings (Wilson and DuBois (21), Blackfan and Wolbach (22), Thatcher (23), Sweet and K'Ang (24)) demonstrate that the process involves the internal organs as well, the principal alterations being the substitution of keratinizing epithelium causing occlusion of ducts and formation of cystic structures. There is some evidence, also, that there may be a direct effect on the secreting abilities of glands. In addition, it appears that pathologic changes suggestive of this condition may be observed postmortem in the absence of the usual clinical features of the disease (Blackfan and Wolbach) and many investigators are now concerning themselves with the sub-clinical phases of the condition (Jeghers (18)), which is supposed to be more common than has been generally suspected. The relation of vitamine A to the formation of rhodospin (visual purple) found in the retinal rods seems well established (Fridericia and Holm (25) among others); and as the rods are most numerous in the peripheral fields of the eyes which are concerned with vision at night, deprivation of the fat-soluble factor leads to a lessened adaptation to diminished light (Chou (26), Jeghers (18)). It also seems to be established that carotene is a precursor of vitamine A and that the conversion takes place under the influence of the liver where the vitamine is chiefly stored. In adults the larger reserves of the fat-soluble factor and the lesser requirements for growth are factors that may account for the lower incidence of the severer forms of the disease; most of the cases observed in the older age-group have been reported in peoples (for example, the Chinese) whose dietary habits are such as to preclude any intake of vitamine A or to restrict ingestion to minimal amounts of it.

The general dryness of the skin, attributed by some to dehydration, undernutrition or intercurrent disease, may be dependent, in part at least, on the specific effect arising from vitamine A deficiency (epithelial, sebaceous gland, sweat gland changes, singly or combined). This symptom, usually encountered early in the disease, is generally the only cutaneous disturbance seen in children. Commonly associated with it is the absence of visible sweating, probably caused by alterations in the sweat glands proper or in their ducts. In advanced form these changes in the skin are considered to be factors in causing the peculiar febrile attacks commonly encountered in the condition, though Sweet and K'Ang (24) believe that a better explanation lies either in the absorption of toxins through altered epithelium or in the metabolic changes that

may ensue from more rapid utilization of fat by the body in an attempt to obtain the fat-soluble factor. In some of the late cases the hair of the scalp is found to be dry, coarse, brittle, manifesting a tendency to fall out; the nails may reveal transverse or longitudinal furrows and are lusterless (Pillat (27)). All the alterations noted respond to the ingestion of vitamine A, provided the changes are not too far advanced (Wilson and Dubois (21), Ross (28)) or there is no severe diarrhea preventing the utilization of the factor, or there is no marked impairment in liver function interfering with the storage of vitamine A and the conversion of carotene into it. These points must be taken into account in evaluating the therapeutic response to ingestion of the fat-soluble factor.

It is believed by most observers that the ocular symptoms constitute the initial manifestations of the disease. There is evidence indicating variability in this general rule. From the clinical point of view Frazier and Hu noted that skin lesions may appear *before the onset of obvious ocular changes*. The close relation between these organs and the analogies between them are illustrated by the alterations in the eyes; the conjunctival epithelium, for example, takes on the character of true skin. There is an increase in its thickness owing to the formation of corneous material and conspicuous kerato-hyaline layer. In adults, moreover, pigmentation occurs in the majority of cases (Mori (29), Pillat and King (30)), attributed to the presence of melanoblasts in the basal layer, and it appears that this phenomenon may have its counterpart in the skin.

Patients afflicted with vitamine A deficiency are considered to be prone to infection only in so far as the changed character of the various epithelial-lined structures of the body may be associated with inability to withstand multiplication of bacteria. The disease may become severe enough to result in death, the most common cause being "bronchopneumonia" secondary to pathologic alterations in the smaller radicles of the respiratory tract.

(b) *Clinical Features of the Follicular Eruption of Vitamine A Deficiency:* It is interesting to note that in 1908, Little (31), on the basis of his experience among the Eskimos, described an endemic of pustular dermatitis or Kallak which resembled scabies owing to the location and manner of spread of the skin lesions coupled with the intense itching; it differed, however, in many clinical particulars, among which may be mentioned failure to respond to sulphur therapy and, on the other hand, cure following the establishment of a relatively normal diet. The condition occurred after the patients had lived exclusively on fish, and notably in conjunction with failure of the berry crop. As suppurative processes are especially common among the Eskimos, the eruption probably represented the result of dietary insufficiency and superimposed infection. The disease did not spread to foreigners who came in contact with the Eskimo, but whose dietary regimen differed. In 1917, Little (32), attributed the condition called Kallak to lack of the fat-soluble factor, the deficiency occurring when the fats derived principally from the seal and the caribou, could not be properly utilized. He also mentioned the case of a shipwrecked white man who came down with the disease in severe form after adopting the re-

stricted dietary regimen of the Eskimos. Among others who have concerned themselves with the cutaneous manifestations of vitamin A deficiency are Stannus (33), Pillat (27), Mackay (34), Nicholls (37) and Goodwin (35). The cases described by Nicolau (17) (1918-19) and the report issued subsequently by his pupil Theodorescu (36) (1928) will receive separate consideration. The outstanding accounts of the peculiar follicular lesions seen in this disease are those of Frazier and Hu (1) (1931, 1936) and Loewenthal (2) (1933), whose clinico-pathologic descriptions have been utilized in this report.

As in scurvy, the dermatosis observed in vitamin A deficiency occurs particularly on the extensor aspects of the upper and lower limbs, to a lesser extent on the abdomen, chest, loins, and buttocks. The face and neck are often involved, especially when the eruption is generalized over the body; the importance of this feature will be discussed in a succeeding paragraph. With the exception of these latter areas, the sites generally spared in vitamin A deficiency are essentially the same as those avoided in scurvy. The eruption may appear rather suddenly and extend rapidly over the areas of predilection. According to Frazier and Hu, it may antedate the occurrence of obvious ocular signs by as long a period as 5 months. The follicular dermatosis is encountered most frequently in adults; in children the cutaneous changes appear to be restricted to general dryness, the explanation for this difference in clinical behavior probably lying in the incomplete state of development of the pilo-sebaceous apparatus in the younger age-group.

The typical lesion is the follicular papule, characterized by the occurrence of marked hyperkeratosis of the hair follicle openings. It varies in size from that of a pinhead to that of a lentil in occasional instances. In many cases there is lack of an accompanying inflammatory element; in other examples superimposed evidence of inflammation is present, though relatively mild in degree. The hyperkeratosis presents itself as a dry, firm, intrafollicular plug which may occasionally project in the form of a spine or it may be covered by loosely adherent scales (Frazier and Hu). When the hand is passed over the affected areas, there is created the impression of "highly accentuated" goose flesh. Expressing the plugs frequently discloses gaping cavities, another indication of the pronounced degree of hyperkeratosis. The immediately surrounding perifollicular zones are often pigmented as a probable consequence of increased melanin pigment in the basal layer of the skin; this phenomenon has its probable counterpart in the conjunctivae of adults afflicted with the disease. The discoloration is, therefore, not caused by the deposition of hemosiderin from extravasations of blood. As in scurvy, but to a greater degree, the hairs in the affected follicles are broken, deformed, or have completely fallen out. It is probable that in many cases these are not replaced owing to the advanced degree of interference with growth, occasioned by pressure atrophy. Itching appears to be variable in incidence and intensity; it was absent or minimal in the cases reported by Frazier and Hu and fairly constant in the patients observed by Loewenthal. Frequently there is associated absence of visible sweating of the skin, a feature of great importance in the evaluation of the effects of specific therapy.

The lesions which are met with on the face are of special importance. Owing to the formation of numerous large "comedones," acne vulgaris is simulated. Unlike the condition in ordinary cases of acne vulgaris, the skin of the face is generally dry (Frazier and Hu (1b)), though exceptions have been recorded by Loewenthal (2); there is little tendency for pustule formation as judged by gross inspection; the cases occur in people beyond the acne age; and the sites of predilection are areas of the body spared in ordinary acne. On morphologic grounds there may be some resemblance to tar or oil acne, which are, however, distinguished by a history of contact with these substances. Bromide and iodide acne show a greater tendency to affect the face and chest than is generally seen in vitamin A deficiency, and the lesions are usually of the inflammatory pustular type. In the accounts of the hemorrhagic follicular dermatosis observed in scurvy, involvement of the face and neck has, thus far, not been recorded, even when the lesions were otherwise widely distributed. Implication of the dorsum of the hands and of the feet, as reported in one unusual instance of vitamin deficiency (Frazier and Hu (1b)), has not been seen in scurvy. The localization of numerous typical hyperkeratotic lesions on the posterior aspects of the elbows is frequently observed in vitamin A deficiency, rarely in scurvy.

In their further development the lesions of vitamin A deficiency, which may persist for months, often undergo involution, with the production of definite depressed atrophic areas surrounded by a narrow zone of pigmentation. These healed areas, probably occurring in the absence of gross secondary infection, may be seen interspersed in small numbers among numerous lesions of more recent origin. It is important to stress that at no time during the course of the eruption is a hemorrhagic component seen as in scurvy.

Regarding the importance of the element of infection, there is much diversity of opinion. It seems to be generally accepted that this may occur secondarily late in the course of the disease and that it is attributable to changes in the epithelium allowing multiplication of bacteria. According to Spense and Mackay, there is a high incidence of "skin sepsis" in vitamin A deficiency as manifested by the association of impetigo, boils, diaper rashes, etc. These observations were made in infants and children and are in need of further confirmation from other sources. On the other hand, there are observers who have not been impressed by the incidence of such complications in this disease (Blackfan and Wolbach (22), Sweet and K'Ang (24)). So far as the follicular lesions are concerned, it seems to be agreed that gross secondary infection of them is rare (Loewenthal) or only present in occasional instances, particularly when there is general undernourishment (Frazier and Hu). When this complication occurs, scars are produced; in occasional instances large ulcerations may result (called dermalacia by Pillat who tried to correlate the phenomenon with keratomalacia), and these lesions may rarely simulate secondary ulcerative syphilids (Frazier and Hu). It is possible that in occasional cases the epithelium of the hair follicles may proliferate to form outpocketings or small communicating pouches that contain collections of pus, but such lesions are relatively uncommon and do not necessarily break down to form ulcers, spontaneous resorption occurring.

Relative to specificity of the follicular lesions seen in vitamine A deficiency, there seems to be excellent evidence, both theoretical and practical, that the eruption is attributable to lack of the fat-soluble factor (Loewenthal, Frazier and Hu). That, however, all such lesions represent the manifestation of lack of this factor, as has been maintained by Frazier and Hu (1b), is a proposal with which there may be some disagreement. Nevertheless, their point is well taken when they question the diagnosis of the case recorded by Theodorescu (36); the occurrence of hemeralopia, followed in two weeks by the appearance of a generalized eruption implicating the face and neck as well other parts; the presence of many small pigmented scars or depressions; the absence of a hemorrhagic component despite the widespread distribution of the dermatosis; the occurrence of numerous "comedones" on the face; the marked epithelial changes on histologic examination coupled with the lack of pronounced alterations in the perifollicular capillaries; the healing of lesions with the formation of pigmented depressed areas are points that appear to argue for the inclusion of the case within the category of vitamine A deficiency, even though there was simultaneous evidence of scurvy in the patient. On the other hand, I am unable to accept in its entirety the interpretation offered by Frazier and Hu that the dermatosis described by Nicolau (17) can only be attributed to vitamine A deficiency. It is true that in the second case recorded by this observer, the patient had hemeralopia, but it is equally true that there was unmistakable evidence of scurvy. It seems more probable, in view of certain atypical features, that there was simultaneous deprivation of both vitamins A and C, though it is my belief that the clinical picture was dominated by manifestations of scurvy. It seems interesting to analyze the basis for this belief, as this question will persistently arise whenever there are multiple deficiencies. The evidence favoring the view relating to lack of vitamine C are the typical clinical symptoms of scurvy; the occurrence of perifollicular petechiae; the failure to involve the face, neck, and scalp in all 40 cases seen by Nicolau, even when the rash was widespread in distribution; the pathologic alterations in the blood vessels allowing diapedesis of red blood cells; the rapid absorption of hemorrhages; and, finally, the healing of lesions without the formation of depressed areas at sites of hair follicles. The atypical features pointing towards superimposed lack of vitamine A are the occurrence of hemeralopia; the relatively greater degree of follicular hyperkeratosis; the presence of epithelial hyperplasia with the formation of outpocketings and small communicating channels in the hair follicles; and the long time required for healing of the keratotic accumulations that remained long after the hemorrhagic manifestations had disappeared. It will be seen, then, that the case recorded by Theodorescu from the same clinic nine years later differed in many clinical and pathologic particulars from the observations originally reported by Nicolau (17). The association of vitamins A and C deficiencies is probably not uncommon, judging from the frequent description of hemeralopia in epidemics of scurvy. It will be of great interest to ascertain the part played by each condition in the evolution and the clinical attributes shown by the follicular eruption, whether or not hemorrhage is present. It is likely that

in some instances it will be impossible to differentiate these dermatoses without observing them for long periods and without the aid of histologic examination, and the difficulties will be the greater as both conditions are combined in varying proportions.

(c) *Pathology*: The outstanding features are those concerned with the epithelium of the hair follicles. Within these structures are found dense masses of cornified cells, occasionally containing the remains of coiled atrophic hairs (Frazier and Hu). The epithelium adjacent to the follicles, and, even at some distance from them, shows evidence of hyperplasia, causing elongation of the rete pegs. As a result of the intense cornification, pressure is probably exerted on the lower parts of the follicles, resulting in atrophy and, probably also, disappearance of sebaceous glands, with replacement by infiltration of lymphocytes. It is interesting that giant cells have not been encountered thus far. Frazier and Hu also recognized a similar obstructing process in the upper parts of the sweat ducts, especially that portion lying within the epidermis; they also noted some degenerative changes in the oil glands proper. In one instance a cyst filled with cornified material was found near a hair follicle. In none of the sections was hemorrhage seen, nor was there evidence of diapedesis of red blood cells; in this respect there is a fundamental difference from the alterations found in scurvy. It is my belief that the depressed areas seen after healing takes place are the result of pressure atrophy occasioned by the dense masses of keratinized material formed in most of the hair follicles in this disease and that this occurs, according to most descriptions, in the absence of frank infection. Collections of pus cells may infrequently be noted in the wall and lumen of the hair follicles and any outpocketings formed by proliferation of epithelium; they may be resorbed spontaneously or be the background for the larger ulcerative lesions occasionally noted in the course of the disease. It has been stated by Loewenthal (2) that the striking blackness of the papule may be the result of a relative increase of melanin pigment per square unit of surface, attributed to the acanthosis and wrinkling of the upper layers of the epidermis; this observer found no increase in the number of dermal chromatophores. It appears, therefore, that the pigmentation seen about such lesions is more prominent clinically and that it is a phenomenon requiring further pathologic investigation.

(d) *Response to Therapy*: The difficulties encountered in submitting patients to a critical therapeutic test as regards specific vitamins have been noted by Frazier and Hu; in treating their original group of cases, a diet rich in all the accessory factors was used. However, by a process of elimination it was shown by Loewenthal (2), with a reasonable degree of certainty, that the missing element in these cases was vitamine A or some fat-soluble factor. Treatment with cod liver oil without changing the remainder of the diet resulted in the disappearance of the follicular lesions in practically all of the 74 patients after a period of some nine weeks. In a critical experiment in two instances Loewenthal was able to eliminate any food containing the fat-soluble factor, substituting instead extracts of vitamine A; xerophthalmia and night blindness were relieved immediately and the skin lesions underwent involution in approximately seven to eight weeks.

When proper therapy is instituted, the first evidence of healing of the skin is usually the reappearance of moisture in the folds of the large joints and about the genitalia; this occurs as early as the second week. There seems to be evidence that this represents a direct effect on the sweat glands proper, rather than one concerned with the replacement of desquamated keratinized epithelium by normal epithelium, a process that would require more time. Ocular lesions begin to heal in from one to two weeks in many cases and may be completely cured in about one month. The follicular skin lesions require, with some exceptions, from 2 to 3 months to undergo complete involution (Frazier and Hu), though delicate "atrophic scars" generally remain at the original sites, surrounded by a narrow zone of pigmentation. It seems, then, that much more time is necessary for the skin to become normal in vitamin A deficiency than in scurvy, the latter requiring about one week to 10 days for resorption of hemorrhage and about 2 to 4 weeks for disappearance of the milder keratotic accumulations. In those cases where several months elapse before the hyperkeratosis is replaced by normal tissue, there is

reason to suspect the additional factor of vitamin A deficiency. Finally, it remains to be noted that in evaluating the results of a therapeutic test in patients suffering from deprivation of the fat-soluble factor, there will be slower healing of all the manifestations whenever there is interference with the absorption of vitamin A or the conversion of carotene into it (diarrhea, liver disease, etc.).

SUMMARY

Following the presentation of two typical cases of vitamin C deficiency, there are presented clinicopathologic data indicating that the perifollicular petechial lesions, pathognomonic of scurvy, are distinguishable from the primary follicular papules seen in patients suffering from lack of the fat-soluble factor. The diagnostic importance of these eruptions and the criteria for their recognition are considered at length. The possibility of both deficiencies coexisting in the same patient is discussed on the basis of a critical evaluation of the literature on the subject, with particular regard to their modifying influence on the attributes of the skin lesions.

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Editorials

WATER BALANCE

WE all recognize the importance of a normal water balance in the body with the avoidance of dehydration on the one hand and of edema on the other. When the sick patient is unable to take sufficient water, salts, and food by mouth, he must be supplied with them in some other way and this treatment may be the chief aid in carrying him over a critical period in his illness.

The exact amount of water, salts and dextrose needed and the way the body uses them is not always appreciated. Water is usually of the first importance, and since all patients unable to take water by mouth are short on food, some dextrose is also needed. The indications for giving sodium chloride are not so simple.

The value of saline solutions for patients who have lost sodium chloride by bleeding, vomiting, diarrhea, sweating, etc., has been well established, but there is a tendency to use routine saline solutions for all parenteral therapy whether sodium chloride is needed or not. In the latter case, salt retention and edema is not uncommon. Malnutrition and sepsis may play an important part in this water retention, but the excessive use of sodium chloride is generally the precipitating factor.

Coller and Maddock* and their co-workers have recently done a useful service in gathering facts about the water requirements and in studying the water exchange of a group of sick surgical patients who were given the commonly used intravenous fluids. They have tried to find out both the amount and kind of such fluids which best supplied their patients' needs.

Some of the arithmetic of normal water exchange is well worth remembering. Let us first consider the amount of fluids. In health, the water content of the body is kept fairly constant by a nice balance between intake and output. Fluids drunk vary from about 800 to 2000 c.c., depending on the weather. The water content of food is often underestimated; on a routine diet the food furnishes about 90% of its weight in water from its own water content, plus the water formed by oxidation, namely about 1000-1500 c.c.

The amount of water lost in the urine is about 1500 c.c. and the amount needed for vaporization from the lungs and skin to control body temperature is about 2000 c.c. The amount lost in the feces is small, 150 c.c. or less. The vaporizing process is little effected by the amount of water available while the kidneys are greatly effected and must excrete waste products in the water which is left after other processes are cared for.

Dehydration occurs on many occasions with low intake of fluid such as the day of a surgical operation and just after it, in periods of nausea or food restriction, and with abnormal losses by sweating, loss of blood, diarrhea, vomiting, fever, etc. When a patient is taking nothing by mouth, nearly all of this 3500

c.c. of fluid must be supplied parenterally; if the patient takes some fluid by mouth this can be deducted from the 3500 c.c. total; if abnormal losses of fluid occur they should be added to it.

When the patient enters a hospital in a dehydrated condition, he must not only receive enough fluid for a normal water exchange, but an extra amount to make up for water previously lost. When water is given to such a patient most of the first day's intake goes to replace fluid previously lost, then water for vaporization is needed, and, last of all sufficient water becomes available for the urine.

Next, let us consider the kind of fluids. Coller and Maddock found that in a group of sick surgical patients receiving 5% dextrose in normal salt (or Ringers) solution, all retained water and gained weight, but when the fluids were given as before but the salt omitted, all promptly lost the water they had retained and the edema disappeared, even with a good water intake. In another group of sick surgical patients given equal amounts of 5% dextrose in distilled water, no water was retained.

It is obvious that warnings about the production of edema with salt solutions are well founded and should be remembered and the only reason gross water retention is not seen more often with the routine use of salt solutions is that they are usually given for only two or three days. When parenteral fluids are needed, the thoughtful physician will avoid mistakes by supplying only the amount and kinds of fluids and salts needed and skillful handling of this problem will often save the life of the very sick patient.

Franklin W. White, Boston, Mass.

PORPHYRINS AND PORPHYRINEMIA

THE porphyrin structure of four pyrrole rings occurs as an essential constituent of the hemins, chlorophylls, and at least some of the respiratory enzymes (cytochrome). While the free porphyrins occur in very minute amounts in living organisms, the biological importance of their derivatives makes it obvious that the study of porphyrin metabolism deserves close attention.

The porphyrins of importance in human metabolism are few in number. Chemically, they differ chiefly in the number of carboxyl groups in the side chains, but these small differences are associated with very marked changes in biological properties. Perhaps the most important porphyrin in man is protoporphyrin which is combined with iron to form the natural hemin of blood and tissues. The porphyrin which appears in the bile and urine of normal individuals is principally coproporphyrin. Hijmans van den Bergh has shown that if the liver is perfused with a solution containing protoporphyrin, coproporphyrin appears in the bile. Since protoporphyrin has a powerful photosensitizing effect, this power of the liver represents an important detoxifying mechanism. Besides copro-

*Frederick A. Coller, Vernon S. Dick and Walter G. Maddock: "Maintenance of Normal Water Exchange with Intravenous Fluids." *J. A. M. A.*, 107, pp. 1522-1526, Nov. 7, 1936.
Walter G. Maddock and Frederick A. Coller: "Water Balance in Surgery." *J. A. M. A.*, 108, pp. 1-6, Jan. 2, 1937.

porphyrin and protoporphyrin, mesoporphyrin and uroporphyrin occur in smaller quantities in living organisms or their excreta.

A complication in the study of porphyrin metabolism is the fact that each of the porphyrin types may exist, at least theoretically, in the form of a number of isomers. However, most natural hemins, chlorophylls, and bilirubin are derivatives of the 3d isomer type (III) and only one other isomer, the I type, occurs naturally. Since protoporphyrin is readily produced in the laboratory by removing iron from hemin which is obtained from erythrocytes, it would seem reasonable to believe that in the body protoporphyrin III would originate from a breakdown of the hemoglobin and, therefore, might, under certain conditions, be present in the blood in relatively large amounts. However, the amount of protoporphyrin as such which can be obtained from blood or red cells is extremely small; it is obvious that the healthy body does not allow the accumulation of this substance. The liver and the kidneys are the most important excretory organs in porphyrin metabolism, and it is significant that many cases of disturbance in porphyrin metabolism involve pathologic conditions in the liver or kidneys.

Recently, it has been found possible to develop methods for the quantitative estimation of the several kinds of porphyrins in urine, bile, and feces. So far, however, similar methods are lacking for use with blood and only qualitative or semi-quantitative estimates as to degrees of porphyrinemia are possible. Protoporphyrin is detectable in the erythrocytes of all humans. Watson has reported reticulocytes very rich in porphyrin. In cases of anemia with good regeneration, Seegal observed in the erythrocytes the characteristic red fluorescence of porphyrins in ultra-violet light. A variety of conditions such as fever, hemoglobin destruction *in vivo*, disturbances in metabolism of muscle cells, diseases of the liver, etc., may lead to an increased production or liberation of porphyrins which may be observed in the increased excretion of these substances. In these cases, in general, an increase in serum porphyrin is not detectable unless the normal excretory powers of the kidneys and liver are interfered with. If the secretion or outflow of bile is disturbed by blockage of the biliary passages, both bile bilirubin and bile porphyrin are increased in the blood stream, and the porphyrin in this case is not protoporphyrin but coproporphyrin. Coproporphyrin is generally found in detectable amounts in the serum of individuals with liver disease if there is a direct van den Bergh reaction in the serum. In patients with total biliary obstruction, the total porphyrin excretion is not altered, but the porphyrin practically vanishes from the feces and appears almost entirely in the urine. An increase in serum porphyrins can originate from the ingestion of foods containing large amounts of porphyrins (blood, muscle, etc.). An increase can also result from an abnormal intestinal fermentation and patients with liver disease in which this occurs may show a striking porphyrinuria.

Another source of increased porphyrin in the serum is from the action of toxic chemical substances such as lead, neo-salvarsan, and many lipid-soluble hypnotics and narcotics, including alcohol. These chemical substances not only result in an increased output of porphyrins, but may cause a formation of porphyrin

beyond the ability of the liver and kidneys to excrete them. For example, lead poisoning occasionally produces an increased porphyrin output in the urine along with a marked kidney degeneration; in these cases there is a striking increase of serum porphyrin of the coproporphyrin III type. It is significant in this connection that when lead compounds are added to liver pulp, hemin is decomposed to protoporphyrin instead of to bilirubin; presumably this same action takes place in the body with the addition of the conversion of the protoporphyrin to coproporphyrin by carboxylation in the liver.

In cases of congenital porphyria and the rare cases of very marked spontaneous porphyria, the harmful effects of the accumulation of porphyrins in the body are easily apparent. With smaller accumulations of porphyrins it is uncertain whether there is any harmful effect, but one must remember that porphyrins, when injected into humans, even in small amounts, can have a highly toxic effect.

It must be clear that we are only entering into our knowledge of this highly complex field, but the fundamental place of porphyrins in the vital processes in the body must give them great significance in the biochemistry and pathology of the human organism.

Ansel Keys and Joachim T. Brugsch,
Rochester, Minn.

DIET AND DIARRHEA

IT always has been, and still is, difficult to establish a rational attitude toward fueling that most efficient machine, the human body. The earliest forms of therapy had to do with the physical procedures of applying heat and massage and of changing from the customary to a different type of food. As these measures are readily available to everyone, the alert individual of not too many scruples as well as the less alert individual who blindly follows any and all notions, has utilized them to establish cures for what ails you.

In no field of medicine has there been such flagrant abuse, such absurdity in ideas, and such preying on gullible minds as in that of diet for gastro-intestinal disturbances. The less accessible a part is for careful study, the greater is the mysticism and the positiveness of advice in prescribing treatment. The weird suggestions that are made and the bizarre substances that are poured into the gastro-intestinal tract in the hope of benefiting persons who are troubled with constipation are really unremarkable in comparison to the limited, inadequate diets that are so characteristically ingested by patients who have diarrhea.

We all know of the suggestions that the sufferer partake only of cooked fruits and vegetables; of no "acid" foods, usually meaning citrus fruits and tomatoes; of no beef, pork or veal; of only puréed vegetables; of no milk or only of boiled milk, and so forth, not to mention the absurdities de luxe, such as the implication that it is a mortal sin to eat fried foods or to mix carbohydrates and proteins. Behind all these silly nonfacts is the germ of truth to which expression originally was given in the proverb, "One man's food is another man's poison"; in place of the proverb we now have the term "allergy."

We have heard so often the vivid description of the lettuce leaf or the dill pickle which erodes, digs, and sandpapers the ulcers of the intestinal tract! And we have been told how pepper and other substances sear and scorch the raw areas! Are these things so? Used as one expects an intelligent cook to use them, can these things actually do harm? The individual who is intolerant to certain foods must be kept in mind, but because some get hives from strawberries we don't condemn their use by all persons. Patients who have chronic ulcerative colitis, and especially the relatives of the patients, have all but swooned when the physician has permitted cakes and sausage for breakfast instead of the routine hot cereal, crisp toast and soft eggs!

Several fundamental facts must be considered in feeding persons who have diarrhea, irrespective of its type:

1. The food must be sufficient in amount. The well nourished individual who is normal in all ways except that he has diarrhea—diarrhea of the "habit" or "nervous" type—should cause no concern. But if the patient is depleted, thin or emaciated, whether the diarrhea is of a deficiency type or is the result of ulcerative colitis, his machine needs a most generous amount of fuel, more than if he were well.

2. The food must be adequate in quality. If the patient is intolerant of those foods which carry essential substances, especially the vitamins, minerals and proteins, then the physician must omit the natural foods and supplement with the now readily available concentrates. Probably he will overdo the feeding of vitamins but with less damage to the patient than formerly was done by giving not enough vitamins.

3. Food must be attractive and palatable. The subconscious fear that to eat much will increase the diarrhea is one great reason why these persons do not eat. Hence, a long period of being given puréed, mushy, messy appearing food more and more curbs the desire to eat. Why it is considered so heinous an offense to flavor with garlic, onion, spicy sauces, and so forth is hard to see. Not that a physician would advise chili sauce as a beverage or a plate of garlic as a meal for a patient who has diarrhea or any other condition; yet is it not absurd that temptingly seasoned foods are considered wrong?

This problem of diarrhea boils down merely to one of common sense. If a patient loses a fourth to a half of his food because of diarrhea, he must be given more, not less; if fried foods bother one patient, nevertheless they are not to be condemned for all, and so forth, and finally, for the physician to reason with himself and with the patient will do much to overcome absurdities in prescribing diets and in treating diarrhea. It remains a mystery how one can withdraw from a pigeon-hole a slip, printed weeks or months previously, and confidently offer that to the patient as "The Diet"; marvelous foresight would be required to know, weeks before a patient was seen, what to feed that patient. If it is justifiable to say that anything to do with the human body should be "tailor-made" certainly that thing is the prescription for his fuel. A rich and abundant variety of foods always is available nowadays but with better understanding of individual intolerances, it is possible to supplement with concen-

trates those substances which must be omitted from the diet.

Philip W. Brown, Rochester, Minn.

INDUSTRIAL PHYSICIANS ANNOUNCEMENT

OF special interest to every physician and surgeon of this country is the program of the American Association of Industrial Physicians and Surgeons 1938 meeting.

To broaden the interest in industrial medicine to the end of minimizing the morbidity and mortality of working people; reducing accidents and the number of deaths or cripples resulting therefrom; removing the hazards of occupational diseases, and keeping more people on the jobs in healthy condition—all these are naturally of vital interest to the physician or surgeon in general practice, for they mean more wage earners to assume and take care of more medical care for their respective families.

Acquaintance with industrial medical problems such as these is increasingly important to every physician and surgeon whether he be exclusively in private practice or identified, in whatever relation, with industrial practice. Thus, he will do well to mark on his calendar June 6, 7, 8, 9, 1938, for this meeting of the American Association of Industrial Physicians and Surgeons, which will be held concurrently with the Midwest Conference on Occupational diseases at the Palmer House in Chicago. The field of industrial medical practice is increasingly prolific of broader opportunities and closer cooperation with physicians and surgeons in every specialty and in every locality.

Scientific and technical exhibits will be a feature of this important and instructive convention, and any reference to exhibits should be addressed to A. G. Park, Convention Manager, 510 North Michigan Ave., Chicago.

PHYSICIAN HONORED

Dr. Anthony Bassler of New York City, has been decorated with the Legion of Honor of France for his work in medicine and gastroenterology.

NEWS NOTE

The medical staff of the Menninger Clinic will conduct its fourth annual Postgraduate Course on *Neuropsychiatry in General Practice*, April 25 to 30, inclusive, at the Menninger Clinic, Topeka, Kansas. The course this year will include a brief introduction to the fields of neurology and psychiatry and a specific application of this knowledge to the large group of cases of psychoneuroses, psychoses and psychogenic and neurological disorders which every physician meets in his daily practice. Suggestions made by those who took the course last year have been embodied in this year's program in order to make it applicable to the most common practical problems of the physician.

As in previous years, several guest speakers, prominent in the fields of neurology and psychiatry, will appear at the evening sessions of the course.

One of the greatest tendencies in the English language is that towards the shortening of words and phrases. Telephone becomes phone, automobile, auto, and "God be with you" is shortened to goodbye. And so, with this first number of the new volume, the last

two words of what was a rather unwieldy name are dropped, and purely for convenience sake, the title is shortened so as to read *The American Journal of Digestive Diseases*.

Editorial Board.

Abstracts

GERBELS, ERNST.

Radical Operation for Cancer of the Rectum with Preservation of the Sphincter Muscles. S. G. O., Vol. 65, No. 4, pp. 528-533, Oct., 1937.

On the basis of the work of Westhues on the spread of carcinoma of the rectum the author states that it is possible to excise a growth in the rectum and save the sphincter and much more often than it is being done today. Westhues found that carcinoma of the rectum very rarely spreads downward from the lower end of the growth and that lymphatic involvement upward rarely extends more than ten centimeters, or above the sacral promontorium. The growth does not extend through the pelvic fascia until very late.

The procedure which appeals most to the author may be of from one to four stages. The first stage is an exploration of the abdomen for distant metastases and the establishment of a colostomy in the left half of the transverse colon. The second stage is resection of the tumor following the Goetze method, which is given in some detail. The third step is the closure of any defect in the rectal wall by means of the skin flap made by the incision. At this time, which may be some months after the second stage, it may be possible to free some of the sigmoid colon and draw it down to make an anastomosis with the lower segment. The fourth stage is closure of the transverse colostomy.

In some instances continuity of the bowel may be made following the method of Makulicz or that of Kuetner, which is very similar.

In otherwise favorable cases the author prefers this method and preserves the sphincter and muscle when the tumor lies one and one-half or more inches above the sphincter.

The age of the patient, constitutional type, length of the sigmoid and other factors must be considered. The decision as to which procedure to follow should be made during operation.

Three figures and a bibliography accompany the article.

N. M. Percy, Chicago.

MAYO, CHARLES W. AND NETTROUS, W. S.

Carcinoma of the Jejunum. S. G. O., Vol. 65, No. 3, pp. 303-309, Sept., 1937.

The authors report an additional 31 cases of carcinoma of the jejunum in which the average age of the patients was 51 years. Twenty of the patients were men, while eleven were women.

The symptoms were cramps and epigastric discomfort with recurrent short episodes of intestinal obstruction. By carefully questioning the patient after operation a typical history may be obtained in almost every case. Anemia, loss of weight and strength, with the symptoms of obstruction, and the finding of occult blood in the stool are very suggestive findings.

While Roentgen findings are not specific they render the diagnosis presumptive by exclusion of the stomach and colon.

Frequently (in 5 of the cases) the diagnosis was obscured by the simultaneous existence of gall stones or duodenal ulcer (in 1 case).

The treatment of choice is resection and entero-anastomosis as was carried out in 15 of the cases reported.

Entero-anastomosis or Gastro-enterostomy may be performed as a palliative procedure. Metastases are a common accompaniment of these tumors and the prognosis is unfavorable.

Three figures, one table and a bibliography accompany the article.

N. M. Percy, Chicago.

BLAIDSELL, P. S.

Pathogenesis of Anal Fissure and Implications as to Treatment. S. G. O., Vol. 65, No. 5, pp. 672-677, Nov., 1937.

Because anal fissure is so poorly understood and is even more poorly treated, and because of the fact that patients relieved of the distress of this exceedingly painful lesion are so grateful, the author has undertaken to clarify the pathogenesis and outline a logical treatment of this condition.

Since the great majority of these fissures lie in the sagittal plane, either anteriorly, or more often, as is the case, posteriorly in the anal canal, it seemed logical to search those points for a peculiar factor either anatomical or pathological. An anatomical factor was found in the Y shaped divergence of certain of the sphincter fibers in their course to the coccyx posteriorly. This same factor to a lesser extent is present anteriorly. Crypts, haemorrhoids and hypertrophied papillae are rarely found at these points.

Severance of the superficial cephalad portion of the external sphincter muscle so as to conform with the Y is the logical treatment. The author uses a light vaseline pack to keep the wound open and has had excellent results in a large series of cases.

A small bibliography and 5 figures showing reconstructions of the anal sphincter mechanisms accompany the article.

N. M. Percy, Chicago.

MCCAUGHAN, J. M. AND COUGHLIN, W. T.

Posterior Gastrojejunostomy—An Unusual Error in Technique. S. G. O., Vol. 65, No. 6, pp. 824-828, Dec., 1937.

The authors review the text books and special monographs dealing with retro-colic gastrojejunostomy and find that not a single one adequately describes the technic of that procedure. They describe that technic and report a case illustrating an unusual error which was corrected.

The case reported is one in which the anastomosis was made on the right side of the middle colic artery and in which the afferent limb of the anastomosis was turned back on the efferent limb and partially obstructed. The procedures necessary to correct the mechanism in their case are described and illustrated. A bibliography accompanies the article.

N. M. Percy, Chicago.

ABSTRACTS

BRUNSWIG, S.

Resection of Head of Pancreas and Duodenum for Carcinoma. Pancreatoduodenectomy. S. G. O., Vol. 65, No. 5, pp. 681-684, Nov., 1937.

The author reports a case of carcinoma of the head of the pancreas for which resection of the duodenum and the head of the pancreas was successfully performed. The operation was performed in two stages. The first stage consisted of (1) Gastro-enterostomy, (2) Cholecystojejunostomy, and (3) Entero-enterostomy. The second stage consisted of excision of the pyloric end of the stomach, and the first and second portions of the duodenum and the head, with a portion of the body of the pancreas.

Post-operatively the patient survived a transurethral prostatic resection on the 20th day, and died on the 85th day following the second stage operation. Necropsy showed diffuse abdominal carcinomatosis, which was not present at the time of the operation.

This operation is reported because it seems feasible that it might be employed in cases of primary malignancy of either the head of the pancreas or the duodenum.

Five figures accompany the article.
N. M. Percy, Chicago.

GRANFIELD, G. P.

A Pharmacologic Study of the Mechanism of Gout. Ann. Int. Med., 11, 651-656, Oct., 1937.

As a result of animal experiments and clinical observations the author concludes that the excretion of uric acid may be modified by the autonomic nervous system. More specifically, the action of atropine on allantoic excretion is mediated through the parasympathetic whereas that on uric acid excretion is mediated by the true sympathetic. Separation of the two components of the autonomic nervous system was accomplished by pharmacological means using ergotamine and atropine.

The data presented suggest that the etiology of gout may well be sought in functional disturbances of the vegetative nervous system involving especially the innervation of the kidney.

Hanes M. Fowler, Fort Wayne.

FEIRO, GEORGE W.

Selenium, a New and Dangerous Hazard to Consumers. Consumer's Digest, 2:1-9, Sept., 1937.

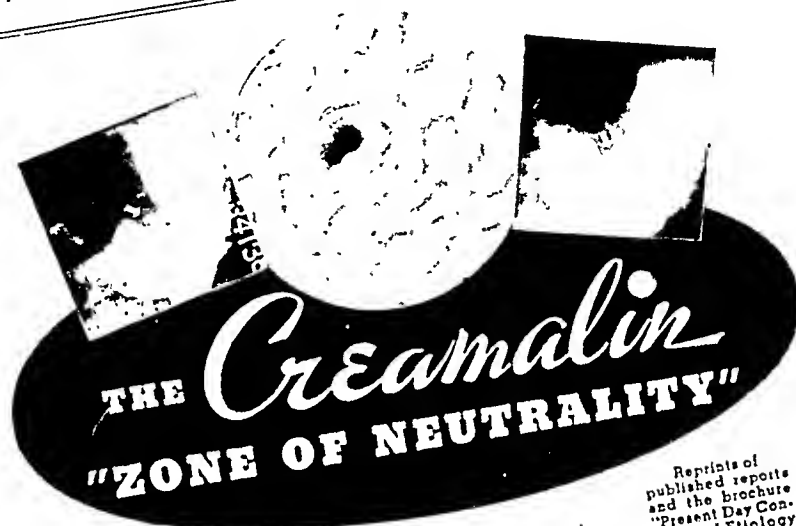
Plants which have grown upon selenium-bearing soil may absorb selenium and certain kinds may absorb very large amounts of this extremely poisonous material and store it in an even more dangerous chemical combination than it was when present in the soil.

Almost any plant growing in such soil may become toxic to some extent.

Plants seem to be able to concentrate the selenium from the soil so that a plant grown on soil containing only one or two parts per million may contain thousands of parts per million. When a plant contains more than four parts per million it is considered dangerous to livestock.

Human beings are exposed to the effects of the poisonous material through the consumption of poisoned animal meat or grain grown upon the selenium-bearing soil. The author deplors the apparent lack of concern on the

part of state and federal departments of agriculture in investigating and reporting on the products of the regions where selenium poisoning of plants and animals may occur. In practically every report of federal or state departments of agriculture the economic loss due to death of live stock is stressed with little, if anything, being said concerning the consumer who eats the poisoned materials. In selenium-poisoned animals the poison is distributed throughout the body, accumulating in largest quantities in the liver. The part of the grain which shows the



Gastrophotor studies of the stomach reveal that Creamalin clings tenaciously to the peptic ulcer crater, covering it with a protective film. Thus a constant zone of neutrality is maintained in the ulcer area, protecting the exposed submucosa and muscularis from the erosive action of gastric juice, and permitting healing to progress unimpeded. These same studies disclose that other antacids, contrary to prevailing opinion, do not adhere to the ulcer.

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greatest concentration is the gluten—a matter of some interest to invalids, since both gluten and liver are in the class of foods often recommended in special diets.

Selenium is a type of poison that produces irreparable harm to the system as demonstrated in laboratory animals and livestock. Liver changes in such animals are comparable to cirrhosis in humans. It has been pointed out that symptoms of selenium poisoning in animals show a marked resemblance to pellagra in man and the onset of the condition may be insidious so that the damage is done before the condition is recognized. A further question of interest is: could the average physician

recognize symptoms of selenium poisoning, particularly chronic poisoning?

The author stresses the fact that the state and federal departments of agriculture have apparently intentionally failed to properly inform the public regarding the existence and danger of use of selenium-poisoned grain and livestock produced in certain regions. In the United States, selenium is found in Arizona, Colorado, Kansas, Montana, Nebraska, New Mexico, Oklahoma, South Dakota, Utah and Wyoming.

A list of references bearing upon the subject is appended to the article.

Hanes M. Fowler, Fort Wayne.

NIXON, JAMES W.

"Primary Carcinoma of the Ileum." *Southern Med. Jour.*, 30:1049-1052, Nov., 1937.

Statistics quoted show that primary carcinoma of the small bowel is extremely rare and that the ileum is especially free from involvement. This is explained by the fact that the fecal contents of the small bowel, as contrasted to those of the large bowel, are liquid, alkaline and practically sterile and at the same time the character of the mucosal cells is such that the effect of the fecal matter becomes a matter of nutrition rather than of irritation.

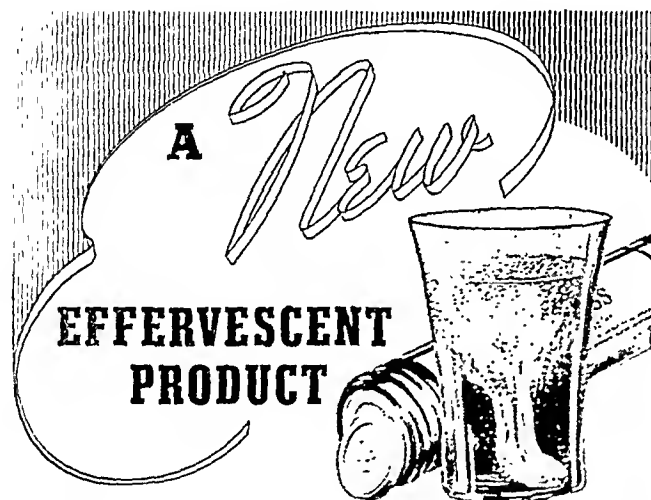
The condition is seldom diagnosed correctly before operation. It is so rare its possibility is usually not considered, the signs and symptoms are quite similar to the more commonly seen conditions, there is generally no mass palpable, and the usual X-ray examinations do not give characteristic findings. Repeated attacks of vomiting and cramps, persistent blood in the stool, marked anemia and exhaustion with negative roentgenological findings should be suggestive of the disease.

The prognosis is extremely bad probably because of the rich lymphatic and blood supply. The rather low average age of the patients, around 44 years, may also be a factor.

The treatment indicated is resection of the tumor and restoration of the continuity of the bowel. While immediate aseptic anastomosis by the Rankin clamp is preferable the condition of the patient may require simple exteriorization and anastomosis at a later date.

A well described case is reported. Although the patient had metastatic mesenteric lymph nodes at the time of operation she was well fourteen months later. A good working bibliography is included.

J. Duffy Hancock, Louisville.



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PESSAGNO, D. J.

"Regional Ileitis with Involvement of the Cecum." *Southern Med. Jour.*, 30:1052-1055, Nov., 1937.

Regional ileitis has a number of confusing synonyms as regional enteritis, chronic non-specific granulomatous ileitis, chronic ulcerative ileocolitis, etc. Since the pathological process is a benign hyperplastic one and since the colon may also be involved the most descriptive and inclusive term would be "chronic non-specific granuloma of the intestinal tract."

No etiological agent has been satisfactorily demonstrated and the appendix can be excluded as a cause. The disease has been described as having four stages: the acute phase with localized peritonitis, the stage of active enteritis, the obstructive stage, and lastly, the stage where fistula formation occurs. Recovery has occurred spontaneously and after a simple en-

terostomy done even in the involved segment. On the other hand the disease has progressed after an apparently complete resection of the involved segment. No case has been reported wherein a fistula has perforated into the peritoneal cavity. In the acute stage the symptoms are suggestive of acute appendicitis which is the usual pre-operative diagnosis. The chronic cases should be more easily diagnosed since a mass can frequently be palpated in the right lower quadrant and X-ray examination may offer suggestive findings. A characteristic sign described by Kantor is "the string sign," a thin irregular line of barium seen in the terminal ileum stopping abruptly at the ileocecal valve and representing the lumen of the thickened contracted intestine.

There is no uniformity of treatment. In children and in cases where the mesentery is not involved an enterostomy may suffice. If the mesentery is thickened and indurated a side-tracking operation may bring about a cure. If it does not, resection, which is used primarily by some surgeons, can be done later.

A most interesting case is reported and an adequate bibliography is included.

J. Duffy Hancock, Louisville.

BEEMAN, J. A. AND HUNTER, W. C.

Fatal Nicotine Poisoning. A Report of Twenty-four Cases. Arch. Path., 24:4-481, Oct., 1937.

The authors report a series of twenty-four cases of death attributed directly to the ingestion of nicotine insecticides. Black Leaf 40, a commercial tobacco by-product containing 40 per cent nicotine sulphate, is widely used for the killing of aphids, a common parasite of the rose plant, and is obtainable without restriction in the local markets. It is probable that this insecticide had been used in most of the cases.

Eight cases came to autopsy. The essential findings were of two types: (1) hemorrhagic gastritis, with or without the odor of nicotine, similar in appearance to the gastritis produced by a mild caustic; (2) cases without gastritis, but showing acute failure of the right heart without an adequate anatomic basis for death. The lungs showed changes commensurate with moderate asphyxia; the kidneys showed a marked hyperemia out of proportion to the acute passive hyperemia elsewhere in the body; a brownish frothy material, similar to that of congestive pulmonary edema was noted about the face and nostrils of the body in nearly all cases.

An experimental study on cavyies with Black Leaf 40 and 40 per cent solution of nicotine alkaloid showed the presence of gastritis only in those

animals given the insecticide. All animals died in convulsions with fixation of the respiratory muscles. The renal hyperemia seen in man was not found in the animals. An attempt to isolate an irritant resin from the Black Leaf 40 as the cause of the gastritis was unsuccessful, but it was concluded that the local irritant action of it was not due to its nicotine content.

N. W. Jones, Portland.

COVELL, W. P. AND WHEDON, M. S.

Effects of the Paralytic Shell-Fish Poison on Nerve Cells. Arch. Path., 24:4-411, Oct., 1937.

The above report is one of a series of studies on mussel poisoning which have been carried out at the George Williams Hooper Foundation, University of California, during the past several years by K. F. Meyer and his associates. Instances of fatal mussel poisoning have been known for years along the west coast of the United States—especially along the mid-coast line of California. The brilliant research of Meyer led to the recognition of a relationship between the appearance of poisoning in man from the eating of mussels and the presence at the same time of a marine dinoflagellate in the sea water upon which the mussels were feeding. The toxic factor acts, after being absorbed from the gastro-intestinal tract, as a depressor of respiration and inhibition of cardiac action; and also, according to Kellaway of Australia, as a "neurotoxin with both central and peripheral actions."

The above study revealed no alterations in the nerve cells of the central nervous system in acutely poisoned animals. In chronically poisoned animals, however, there were changes in the large nerve cells of the ventral horn of the spinal cord and the ganglionic cells of the medulla. The mitochondria were normal in appearance in the nerve cells but showed definite damage in the convoluted tubules of the kidney. It seemed probable that the changes in the nerve cells of the medulla and spinal cord were due to a direct central action of the poison. The slow elimination of the poison from the kidneys may be responsible for the alterations in the mitochondria of the tubule cells of the latter. It is possible also that further study will reveal early changes in the peripheral nervous system, in particular the end organs, to explain the parasthesias which appear early in clinical cases of mussel poisoning in man.

N. W. Jones, Portland.

HURST, A. F. AND KNOTT, F. A.

Regional Colitis. Guy's Hospital Reports, 87:187-198, April, 1937.

Regional colitis is an uncommon condition, in which typical ulcerative

colitis is present in a localized area of the colon which does not include the lower part of the pelvic colon and rectum.

The symptoms are those of ulcerative colitis, but the sigmoidoscope shows a normal mucous membrane. The area of colon involved can be accurately localized with the X-rays after an opaque enema.

Two cases of regional colitis are reported, one in which the proximal half of the pelvic colon was involved and responded very well to medical management. In the other, the descending and iliac colon were involved and recovery followed removal of the affected area. Bacterial investigations led the authors to conclude that the latter case was a result of infection with *B. asiaticus*, the cultural and other characteristics of which are described.

Hanes M. Fowler, Fort Wayne.

COLBECK, J. C., HURST, ARTHUR F. AND LINTOTT, G. A. M.

Regional Ileitis (Crohn's Disease). Guy's Hospital Reports, 87:175-186, April, 1937.

Two cases of regional ileitis (Crohn's disease) are reported. In the first, recovery followed a short-circuiting operation without excision of the affected bowel. In the other case recovery followed resection of the involved area. Complete pathological and bacteriological reports of the specimen are presented. There was no evidence whatsoever from the bacteriological study to indicate that tuberculosis had any etiological relationship with the condition. Typical tubercle-like lesions were observed microscopically in the specimen.

There are two plates showing X-ray pictures of the condition, one plate showing the gross specimen, and two plates showing microphotographs of the tubercle-like lesions in the wall of the involved bowel.

The symptoms of the disease are discussed briefly and a plea is made for the observance of a reasonably restricted conception of Crohn's disease and of the grounds on which such a diagnosis can justifiably be made. The good prognosis resulting from suitable treatment is emphasized.

Hanes M. Fowler, Fort Wayne.

HILL, M. R., BARNES, R. W. AND COURVILLE, C. B.

Vesical Dysfunction Following Abdominoperineal Resection for Carcinoma of the Rectum. J. A. M. A., 109:1184, Oct. 9, 1937.

Resection for carcinoma is not infrequently complicated by bladder distention and retention of urine. As a result of continued obstructive or paralytic obstruction, cellulose or small diverticula may appear. The urinary

retention is variable in duration. It may be transitory or at times it is permanent. The extent and duration of vesical dysfunction depends on the amount of damage to the nervous elements. The fact that the parasympathetic elements are predominantly affected suggests that the pelvic nerves or parasympathetic elements in the hypogastric plexuses are the seat of the injury. The relation between the pelvic nerves and hypogastric plexuses and the lower part of the rectum penetrating the pelvic floor has been shown by anatomic dissections. If the upper part of the rectum or the lower part of the sigmoid flexure is involved, or if there is extensive affection of the regional lymph nodes with fixation of other organs or tissues, these nerve injuries are more apt to take place.

If there is more than 50 c.c. of retained urine an indwelling catheter should be used. Cystitis most often develops in patients who are not catheterized. It is treated by lavage of the bladder with potassium permanganate solution (1:6,000) and instillation of 15 c.c. of silver nitrate solution (1:1,000).

Francis D. Murphy, Milwaukee.

ABELL, I.

Acute Abdominal Catastrophies.
J. A. M. A., 109:1241, Oct. 16,
1937.

When the symptoms of acute ab-

dominal catastrophies are encountered the determination of whether or not the condition is operable is of utmost importance and often very difficult. Prolonged pain, nausea, vomiting and constipation generally indicate a surgical lesion, while diarrhea most often indicates a medical condition. A careful history and complete physical examination with blood and urine analysis should always be done in an effort to distinguish a medical from a surgical ailment.

Appendicitis is responsible for about 50 per cent of the emergency abdominal operations. Diagnosis is easy in typical early cases, however, if the patient is seen late, or if the appendix is in an atypical position there may be difficulty. In infancy and childhood recognition is hard. Pain, nausea, vomiting, fever, and leucocytosis should put one on guard. If gangrene or peritonitis has developed, the author considers that, after restoration of fluid, the necrotic, virulent tissue should be removed without undue trauma.

The high mortality rate in intestinal obstruction is due in a large measure to delay in operation. The site and character of obstruction is also important in prognosis. External obstructions, strangulated hernias, offer no diagnostic problem, but internal obstructions are hidden from view and obscure to palpation. Abdominal pain, nausea, vomiting, constipation with the

absence of fever and leucocytosis are suspicious signs, and audible or visible peristalsis with roentgenogram interpretation of fluid and gas levels are often diagnostic before the patient's condition becomes extremely grave. Fluids must be replaced and resistance may be built up by transfusion before operation. The type of operation must be suited to the lesion and the patient's condition. In infancy intussusception is the common cause of obstruction, in early adult life there may be hernia and peritoneal adhesions, and in later life carcinoma is the greatest causative factor.

If peptic ulcer is present perforation or hemorrhage demand emergency treatment. Acute perforations give rise to agonizing pain, nausea, vomiting, board-like abdominal rigidity, and sometimes shock. To delay operation is disastrous.

Diverticulitis in Meckel's diverticulum occasionally causes an acute abdominal catastrophe and there may be diverticula elsewhere. The symptoms closely mimic those of appendicitis.

Acute pancreatitis is infrequent and very similar in symptoms to perforated ulcer and cholecystitis, and therefore it is often not diagnosed. There are no pathognomic symptoms. Vomiting, pain, and collapse are encountered. Previous gall bladder disease, pain radiating from the right costal margin across the upper abdomen, tenderness over the

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pancreatic area, pain left of the upper midline, and a mass in the pancreatic area are helpful diagnostic signs when present. Prompt operation is necessary to relieve torsion, stop hemorrhage, prevent leakage, and afford drainage.

Ruptured ectopic pregnancy is not difficult to recognize. There is sudden pain, vomiting, faintness, anemia, collapse, rapid pulse, subnormal temperature. The author rehabilitates the patient with transfusion and operates immediately.

There is still difference of opinion about the treatment of acute cholecystitis. Atypical cases are confused with appendicitis, leaking peptic ulcer and pancreatitis. Gangrene and perforations are surgical emergencies, but delayed operations in inflammations are advised by some. The author, however, considers that operation should be done immediately because delay invites complications. Dextrose should be given, deviations in the blood chemistry corrected and the balance of body fluids restored before operation.

Francis D. Murphy, Milwaukee.

MARSHALL, S. F. AND KIEFER, E. D.

Partial Gastrectomy for Gastric or Duodenal Ulcer. J. A. M. A., 109:1341, Oct. 23, 1937.

The advisability of subtotal gastrectomy for gastric and duodenal ulcer is a controversial subject. It is impossible for one method to fit every patient and type of ulcer. 242 patients operated on for ulcer at the Lahey Clinic were studied. Preoperative determination of the type of ulcer is valuable so there should be a period of medical treatment and repeated X-ray examinations before operation. The selection of the type of surgical procedure is a complicated problem.

In partial gastrectomy the mortality rate is high. In the Lahey Clinic the policy in treating ulcer cases has been conservative, operation being done only when medical treatment was unsatisfactory or complications occurred. Subtotal resection more nearly meets the requirements for treatment—prevention of complications and recurrences—than any other procedure, but the hazards of the operation are great. The technic is described. The preoperative and postoperative management are of great importance. It is important to strive for post-operative acidity because of the occurrence of jejunal ulcer when the acid is not sufficiently reduced by partial resection. Unless acidity or hypo-acidity is produced, it is difficult to see any clinical advantage of this operation over gastro-enterostomy. In general the period of convalescence is extended. The final clinical results are quite satisfactory. In the series of 102 patients on whom gastric resection was done, 84 per cent are in good or excellent

condition, 9 per cent have symptoms caused by functional disorders, and 6.7 per cent have had postoperative ulcer.

Francis D. Murphy, Milwaukee.

BROWN, P. W. AND MARCLEY, D. M.

Prognosis of Diverticulitis and Diverticulosis of the Colon. J. A. M. A., 109:1328, Oct. 23, 1937.

The authors studied 596 patients with diverticulitis and diverticulosis of the colon at the Mayo Clinic and follow-up data were obtained in 86 per cent of the series. The symptoms observed were diarrhea, bleeding, inflammatory and obstructive symptoms, purulent rectal discharge, and fistula of the bladder. These may be lacking, moderate or severe. Ninety-nine patients were treated surgically. Fifty-seven recovered and 43 per cent either died after operation, or continued to have intestinal trouble. Medical treatment consists of rest, application of heat, dietary regulation and oral administration of olive oil. This regimen was used in 227 cases. Sixty-three per cent recovered, but in 37 per cent the results were only fair or poor. By regulation of diet and adhering to a definite regimen, however, many could live in comparative comfort and minimize the frequency and severity of the attacks. No evidence of a direct relation between carcinoma and diverticulitis was found.

Francis D. Murphy, Milwaukee.

GOLDEN, R.

Antral Gastritis and Spasm. J. A. M. A., 109:1497, Nov. 6, 1937.

Gastritis may be generalized throughout the entire stomach, but often it is limited or has its maximum effect in the antrum. This has led to the terms "antral gastritis," "pyloritis" or "pyloric gastritis." The symptoms may be the same as those of peptic ulcer including hemorrhage; or pain, vomiting and weight loss may suggest malignancy. The diagnosis depends on gastroscopic and X-ray examination.

This type of gastritis is associated with the "prepyloric syndrome." The involvement of the deeper layers of the stomach by inflammation probably accounts for the following physiological and anatomic changes: (1) prepyloric narrowing of varying degrees due to spasm, (2) abnormal, stiff, irregular peristalsis, (3) exaggeration, diminution or absence of mucosal folds, (4) hypertrophy of the pyloric muscles, (5) shallow mucosal erosions which are not demonstrable by X-ray or penetrating ulcer of the lesser curvature, (6) delay in emptying, sometimes resulting in a twenty-four hour gastric residue.

There is difficulty in the differentiation of antral gastritis from carcinoma. The most important differential point

is the demonstration of mucosal folds in the narrowed area which should be obliterated by infiltrating carcinoma. If atrophic gastritis has caused thinning of the mucous membrane, diagnosis is very difficult. A definite palpable mass is evidence in favor of malignant disease. The author has found repetition of examination after several days of lavage helpful, especially if definite stasis is present. If there is doubt, operation is advisable.

Francis D. Murphy, Milwaukee.

LAHEY, F. H.

The Management of Pulsion Esophageal Diverticulum: Based on an Operative Experience with Eighty-two Cases and a Follow-up Study of Fifty-three Cases. J. A. M. A., 109:1414, Oct. 30, 1937.

Pulsion diverticula far outnumber all other types of esophageal diverticula. A pharyngo-esophageal diverticulum is a protrusion of the mucosa through the muscular wall of the hypopharynx. The sac lies between the pretracheal and prevertebral fascia and its neck is surrounded by fibers of the inferior constrictor muscle and the cricopharyngeus muscle. The symptoms are accumulation of food in the sac and related obstruction to the passage of food into the esophagus. There are difficulty in swallowing, regurgitation, gurgling noises in the neck, choking, attacks of strangling or coughing, and loss of weight. Successful operative treatment involves complete removal of the sac and its neck, the protection of the patient from the development of cellulitis between the prevertebral and pretracheal fascia and extension of infection into the mediastinum. The author uses the two stage operation because it guards against leakage of contaminated esophageal contents into the mediastinum with consequent mediastinitis. In the series reported there were two failures, two who showed poor results and forty-nine who recovered.

Francis D. Murphy, Milwaukee.

WATSON, BERNARD A.

Clinical Significance of Glycosuria. Jour. Lancet, 58:1-4, Jan., 1938.

The incidence of glycosuria on routine examination is 0.5 to 2.0%. Sixteen to 20% of patients showing glycosuria are found to have disturbed glucose metabolism as judged by the glucose tolerance test. Regardless of the cause, glycosuria only occurs either in the presence of a lowered renal threshold for glucose or an elevated blood sugar, e.g., above renal threshold for glucose.

A simple fermentation test to differentiate glucose from other reducing substances is given. It is pointed out that excess of certain normal constitu-

ents in the urine may give a positive reducing test, as well as certain drugs that are listed.

Determining whether glycosuria is transient, post-prandial, or persistent, will aid in determining the severity of the underlying causes. Glucose tolerance tests done under carefully controlled conditions are an invaluable adjunct to the early diagnosis of a disturbed carbohydrate metabolism. If

fasting and 2½ hour blood sugars are the same, regardless how high the others may go, it is unlikely that diabetes exists. Figures for normal glucose tolerance tests and the more common variations are given. Early diagnosis of diabetes mellitus means early treatment with a better prognosis.

Hanes M. Fowler, Fort Wayne.

KEETON, ROBERT W.

Clinical Problems in Diabetes. Illinois Med. Jour., 73:31-38, Jan., 1938.

The author stresses the importance of educational training of diabetics with regard to the proper use of diet and insulin. Diets should be prescribed in the proper amounts just as drugs are prescribed in the proper dosage. Converting the diet prescription into an acceptable diet requires knowledge of foods and falls in the field of dietetics.

Several cases are cited illustrating the advantages of the use of protamine insulin.

Complications frequently seen in diabetics whose diets have been deficient in certain food elements are, a pellagra-like syndrome with uncontrollable diarrhea, and peripheral neuritis. These conditions respond to the adequate use of vitamins B₁ and B₂, respectively.

Diabetics with impaired peripheral circulation should have bed rest and treatment designed to facilitate the establishing of collateral circulation such as constantly controlled heat.

In cases of gangrene early adequate amputation is the treatment of choice. In cases where delay seems advisable, particular attention must be paid to care of the affected area. The surrounding temperature should be lower than body temperature to lessen autolytic digestion.

Hanes M. Fowler, Fort Wayne.

ABELL, IRVIN.

The Treatment of Peptic Ulcer. Ann. Int. Med., XI, 762, Nov., 1937.

The problem is recognized by the author as a medical one, primarily. Complications, sequelae and intractable chronicity constitute a triad, giving it a surgical aspect. When surgical interference is thought to have become necessary, a quiescent state of the ulcer makes the operation a safer one. The type of operation should be determined by the conditions and complications found at laparotomy. Massive resections have not been done on the basis of removal of the acid-bearing portion of the stomach. The selection of the case for operation, the author thinks, is the joint function of the physician and the surgeon. Perforations should be closed immediately. 80 per cent of duodenal perforations occur on the anterior wall and 90 per cent of acute perforations of stomach ulcers are found on the lesser curvature of the pre-pyloric portion of the stomach; perforation on the posterior wall is often sealed with adhesions.

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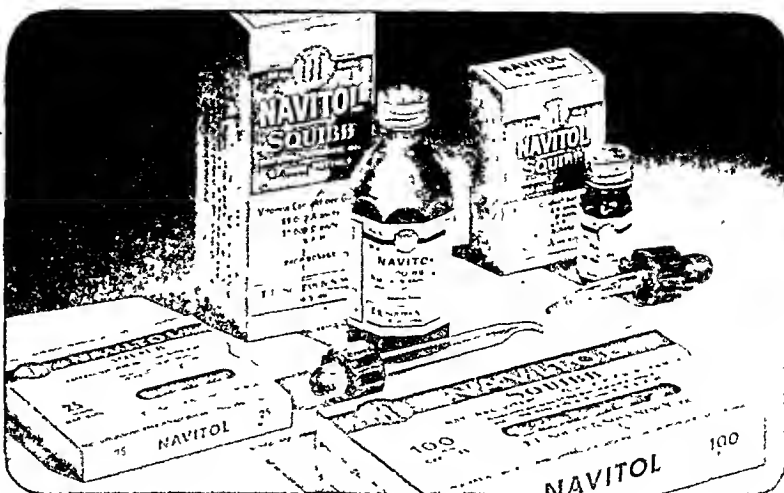


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eradication avails. Malignant degeneration of duodenal ulcer is not expected and hence chronicity scarcely constitutes a reason for surgical interference. Gastro-enterostomy is ranked as an infrequent procedure in dealing with duodenal ulcers because eradication of the ulcer is not deemed imperative; when eradication must be done the cautery method of Balfour is preferred with a posterior gastro-enterostomy. Malignant changes are common enough in ulcers of the stomach, hence removal or destruction of the ulcer is advocated.

Various types of operative procedures are discussed. The opinion is expressed that with proper selection of patients for operation, judgment in choice of procedures combined with proper supervision for at least a year after operation offer good prospects for relief.

Without qualifications the author concludes with the statement that "in the vast majority of patients presenting gastric symptoms, the latter are

due to causes extrinsic to the gastric tract."

Virgil E. Simpson, Louisville.

PORTIS, S. A. AND JAFFE, R. H.

A Study of Peptic Ulcer Based on Necropsy Records. J. A. M. A., 110:6, Jan. 1, 1938.

Although there is much literature on the surgical and clinical aspects of peptic ulcer, necropsy studies are few. The authors have studied the incidence of peptic ulcer in 9,171 consecutive necropsies performed at Cook County Hospital, Chicago, from 1929 to 1936.

There were 457 cases of peptic lesions, or a total of about 5 per cent. The incidence of ulcers was greater in white people than in negroes and more were found in white males than in white females. The ulcer was active in 339 of the 457 cases, and 118 instances it was the essential lesion. In almost twice as many it was incidental. The site of the ulcer was the duodenum most often when it was the essential lesion and gastric ulcers were more common in the incidental cases. In the male most ulcers occurred between the ages of 51 and 60 years and in the female two peaks were found—31 to 40 years and 61 to 70 years. When peptic ulcer was the essential lesion death was caused by hemorrhage in 18.3 per cent of the cases, perforation in 20 per cent of the cases, and stenosis in 7.5 per cent. Hemorrhage was more frequent in the stomach and perforation occurred more often in the duodenum.

The greatest incidence of peptic ulcer coincides with the age period when arteriosclerotic changes take place. In those cases where ulcer was an incidental lesion, it most frequently accompanied cardiovascular disease. It is concluded, too, that gastric ulcer tends to be acute while duodenal ulcer is more often chronic.

Francis D. Murphy, Milwaukee.

SPRUNT, T. P.

Cirrhosis of the Liver. J. A. M. A., 109:1945, Dec. 11, 1938.

The most valuable information for the diagnosis of hepatic disease is obtained by careful clinical history and physical examination. In some cases liver function tests are desirable; however, there is no single reliable test. One of the most important clinical signs is jaundice. When liver function is oppressed urobilin accumulates in the blood. Urobilinogenuria is an indication of depressed liver function. Jaundice may be of the retention type (bilirubin accumulates in the blood and given an indirect van den Bergh reaction) and the regurgitation type (bile escapes into the tissue spaces and blood sinusoids due to obstruction or necrosis and given a direct van den



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	eradication avails. Ma	
	tion of duodenal ulcer	
	and hence chronic	
	ing OXYGEN INTO THE ISOLATED COLON OF A PATIENT WITH CHRONIC ULCERATIVE COLITIS	Jacob Buckstein, M.D.
	tutes a reason for	
	Gastro-enterostomy	G. M. Dacl, M. D. and Lester R. Dragstedt, M.D.
	frequent procedure	
	ORANGE JUICE ON GASTRIC ACIDITY	Charles Dimmler, Jr., A.B.
	duodenal ulcer	
	INSULIN AND THE HIGH CARBOHYDRATE LOW FAT DIET IN DIABETES MELLITUS	
	the ulcer is	
	when eradicated	Seale Harris, M.D. and Seale Harris, Jr., M.D.
	cautery	
	BILIC COLLOIDAL DIET	F. M. Pottenger, Jr., M.D.
	Mal	
	BILIARY TRACT LESION OF DUODENAL ULCER	Norman W. Elton, M.S.
	PLASTIC ACIDITY IN CHICKS WITH EXPERIMENTAL GASTRIC ULCERS	Garrett Cheney, M.D.
	SOME RECENT ADVANCES IN THE PHYSIOLOGY OF GASTRIC SECRETION	B. P. Babkin, M.D., D.Sc., F.R.S.C.
	REPORT OF AN APPARENT CASE OF SECONDARY PELLAGRA	M. B. Holoman, M.D. and Homer I. Silvers, M.D., F.A.C.S.
	A CASE OF PEPTIC ULCER IN A CHILD FOLLOWING BRAIN INJURY	
		Frances R. Vanzant, M.D. and James A. Brown, M.D.
	UNUSUAL HEMATEMESIS OF GASTROENTERIC ACID. HEREDITARY HEMORRHAGIC TELANGIECTATIC DYSPLASIA WITH GASTRO-	
	TAXIS OF STOMACHORRAGIA	Hyman I. Goldstein, M.D.
	THE ACTION OF HISTIDINE ON THE GASTRO-INTESTINAL TRACT	Louis S. Goodman, M.D. and Philip A. Bearg, M.D.
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Young Stomachs— and Old

Would it not be a reasonable analogy to say that the digestive organs of a newborn infant and those of an adult afflicted with a digestive disorder are in a sense quite similar?

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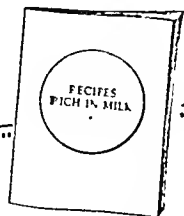
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Bergh reaction). The former and milder form accompanies hemolytic anemia, congestive heart failure, malaria, and lobar pneumonia. The latter is associated with the major acute hepatic disorders. Ascites and a palpable spleen are usually obvious clinical conditions. When spontaneous diuresis occurs it is a favorable diagnostic sign. The disturbance in fluid balance may be related to reduction of the blood plasma proteins. Some students consider hypo-albuminemia an indication of hepatic insufficiency. The size of the

liver is important. It is enlarged in portal cirrhosis and decreased in toxic cirrhosis. Because of the great reserve power of the liver, function tests are important when the lesion is diffuse and widespread. The estimation of bile pigments in the urine, stool, duodenal contents and blood serum and the van den Bergh test for bilirubin in the blood stream are the most valuable aids. Other tests, excretory, carbohydrate tolerance, and protein metabolism, may be valuable in some situations.

Of the several kinds of cirrhosis, portal, toxic, pigmentary, and biliary, the portal type is the commonest. It is easily diagnosed by distended abdomen, firm edges of the liver, palpable spleen, dilated thoracic and abdominal veins, anorexia, nausea, coated tongue and offensive breath. There may be hematemesis and melena and secondary anemia. The urine is scanty and contains urobilinogen and mild jaundice is often present. The van den Bergh reaction and the excretory function tests are positive. In the earlier stage there is malaise, headache and depression and later delirium, drowsiness and coma are common. Depletion of liver glycogen reserve, pregnancy, toxic thyroid states, syphilis and its treatment and alcohol may all be etiological factors.

In treatment, the cooperation of the patient is important. Alcohol and irritating foods such as spices, condiments and pickles should be eliminated. The intake of protein should be cut to one gram per kilogram of body weight. Meat must be cut down and no fried foods are given. The diet must be high in carbohydrates. Cereals and starchy vegetables and dextrose in fruit juices are important. Sufficient rest and mild exercise are necessary. Other accessory methods of therapy such as iodides and calcium may be used and particular situations such as bleeding esophageal varices demand special attention.

Francis D. Murphy, Milwaukee.

WALTERS, W., MCGOWAN, J. M., BUTSCH, W. L. AND KNEPPER, P. A.

The Pathologic Physiology of the Common Bile Duct. J. A. M. A., 109:1591, Nov. 13, 1938.

In patients with lesions of the biliary tract, morphine, codeine and dilaudid produce a marked increase of pressure within the common bile duct because they produce a spasm in the sphincter at the lower end of the bile duct. The resulting biliary colic may be relieved by amyl nitrite, glyceryl trinitrate, and theophylline with ethylenediamine.

The authors suggest the use of morphine as a diagnostic measure. If an attack of pain which is relieved by glyceryl trinitrate results the evidence is in favor of some disturbance in the sphincteric mechanism at the lower end of the common bile duct either with or without stones. It is, however, valuable only as a temporary measure until the common duct has been explored.

Francis D. Murphy, Milwaukee.

CRONIN, B. B. AND BERG, A. A.

Right-Sided (Regional) Colitis. J. A. M. A., 110:32, Jan. 1, 1938.

In about 90 per cent of the cases of ulcerative colitis the lesion begins in

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the rectum or lower sigmoid and spreads to the proximal segments, the descending and transverse colon and in severe cases eventually to the hepatic flexure, ascending colon, cecum and terminal ileum. In a certain percentage of cases, however, the lesion may begin in the hepatic flexure or ascending colon and involve the right side of the colon in a regional or segmental distribution, spreading to the more distal segments. Spontaneous recovery is rare in these cases.

The authors studied seventeen cases

of right-sided colitis and found them to be uniform in their outstanding characteristics. The two forms of ulcerative colitis are similar in general characteristics. Etiologically and pathologically they are the same. In right-sided colitis the course is less severe but it is progressive. The diarrhea is not as troublesome, involvement of the skin, buccal mucosa and joints is rare, and rectal complication less frequent. In right-sided colitis medical treatment is ineffective but permanent cure can

be obtained by surgical intervention without a disproportionate risk.

Undoubtedly, in the past, this type of colitis has often been overlooked, and with greater recognition its incidence will rise to greater than 10 per cent.

Francis D. Murphy, Milwaukee.

EDWARDS, MONTE.

"The Management of the Ano-Rectal Syndrome of Lymphogranuloma Inguinale." *Southern Med. Jour.*, 30:1194-1197, Dec., 1937.

While the clinical manifestations of lymphogranuloma inguinale are well recognized diagnosis should always be confirmed by the specific Frei test. In the ano-rectal region the onset of the disease may be fairly acute and febrile or relatively insidious but in either case there is congestion and edema of the rectal mucosa with a varying amount of purulent or sanguino-purulent discharge. Accompanying this irregularly shaped circumscribed elevated areas can be palpated. Constitutional symptoms may vary from practically nothing to pronounced weakness from toxemia and bleeding. Painful inflammatory swelling of the anus with or without fissure, may occur. Infiltration, suppuration, and necrosis proceed in a disorderly fashion and some tendency to cicatrization is always present. Cicatrization of course leads to stricture formation which is the nearest thing to arrest that can occur in the disease.

In the evaluation of medical measures it must be borne in mind that in spite of apparent intractability there is sometimes a tendency to temporary arrest. Bed rest is indicated at those times constitutional symptoms are present. The chief indication for surgical measures is the relief of the stricture. While complete obstruction rarely results absorptive phenomena accompanying the stricture will demand its treatment. Procedures used begin with periodic dilatation which may be very satisfactory, and include internal proctotomy, side-tracking the fecal current by a colostomy, and in some instances excision of the rectum. Colostomy should not be done without careful exploration of the left colon as the extent of the distase may necessitate placing the opening in the transverse colon. Since the disease is a progressive one the colostomy will in many instances be only palliative as in anorectal malignancy. Therefore, in selected cases, especially where the invasion is of the progressive hyperplastic type, or where improvement after colostomy is unsatisfactory a radical excision by either the perineal or abdomino-perineal route seems well justified.

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BUNCH, GEO. H.

"Acute Phlegmonous and Non-Traumatic Perforative Lesions of the Colon." *Southern Surgical*, 6:449-457, Dec., 1937.

While the diagnosis and treatment of colitis and colonic ulcer are ordinarily medical acute phlegmonous inflammation and acute perforation of the colon are surgical emergencies. Such cases are quite rare and none of the four reported was correctly diagnosed before operation. One patient who had an incisional hernia at the scar of a previous appendectomy was thought to have an incomplete intestinal obstruction. Operation disclosed a diffuse peritonitis of undetermined cause which at autopsy was found to be due to perforation of a simple ulcer of the upper rectum at the peritoneal reflexion. A second case was diagnosed as one of spreading peritonitis probably from a ruptured viscus. At operation the general peritonitis was found to be complicated by a massive hemorrhage, a most unique occurrence. The descending colon near the splenic flexure was dark and discolored about a perforated ulcer and the bleeding was from a vein in the necrotic omentum near its attachment to the colon. The third patient was thought to have a diffuse peritonitis following a perforated appendix. Laparotomy showed a

massive phlegmon of the anti-mesenteric border of the ascending colon the appearance resembling a series of large confluent carbuncles in the gut wall, each with multiple erasers. Perforation of the bowel occurred during the operation and was followed by a fecal fistula and general improvement. However, on the 16th post-operative day the patient died of a right subphrenic abscess. The fourth patient was thought to have an acute appendicitis but at operation there was found an acute phlegmonous inflammation of sigmoid from acute diverticulitis. Recovery followed simple drainage but four and a half years later death followed a general peritonitis due to a perforated diverticulum in this area.

The resistance of the colon to the pathogenic bacteria it harbors is due to an immunity gradually acquired during life and when impaired inflammation and ulceration occur. Ulcers may result from mixed infections by unidentified organisms, may be due to specific organisms as occur in tuberculosis, syphilis, amebic dysentery and typhoid fever, may complicate systemic diseases or may follow thrombosis, embolism, or trophic changes in the gut wall.

Ulcers with marked tendencies to perforate have distinctive characteristics. In the beginning the lesion, though often multiple, is always acute,

clean cut and penetrating without undermining. Most cases are symptomless and unless the ulcer is in the lower rectum or about to perforate the pain is not severe and there is little tendency to bleed.

Phlegmonous inflammation in the colon may probably follow mechanical injury to the mucosa such as could occur from fish bones swallowed with foods. There are no pathognomonic symptoms; the ideal treatment indicated is resection if technically possible, drainage of the affected loop if not. In the sigmoid the phlegmonous inflammation is often due to diverticulitis, the involvement is usually segmental, perforation is rare, and while these are the cases best suited for resection they tend to resolution and spontaneous relief when treated by conservative surgical measures.

J. Duffy Hancock, Louisville.

LINEBERRY, E. DICE AND ISSOS, D. N.

"Treatment of Massive Hemorrhage from Duodenal or Gastric Ulcer." *Southern Med. Jour.*, 30:1228-1230.

Approximately one-third of patients with gastric or duodenal ulcers give a history of one or more hemorrhages. Since recovery without specific alterations in diet or habits is not uncommon conservative management must be

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carefully considered and surgical interference but rarely undertaken.

The usual treatment for hemorrhage consists of rest, morphine, ice-bag to abdomen, for five days or until the hemorrhage has stopped. Smithies preferred local heat to cold applications but neither measure is probably of any value beyond helping to keep the patient quiet and assure him that something is being done. While the starvation treatment is generally accepted the authors believed that food and alkalization as advocated by a few others was more rational. This treatment is based upon the view that frequent ingestion of small amounts of bland food causes less peristaltic action than hunger in an empty stomach and that frequent ingestion of alkalies and bland food would tend to neutralize the gastric acids, dilute the digestive juices and thus both prevent the digestion of the clot at the bleeding point as well as promote the healing of the ulcer.

The essentials of the plan of treatment used very successfully in a series of thirty-eight cases are as follows: (1) complete bed rest; (2) three to four ounces of cream and milk every hour from 7:00 a. m. to 9:00 p. m., started immediately unless contraindicated by vomiting or shock; (3) ten

one-fourth dram doses daily of an alkaline powder given in three or four ounces of water on the half hour between milk feedings; (4) instead of morphine which frequently excites nausea and vomiting and probably increases gastro-intestinal peristalsis, two grains of sodium-phenobarbital given intramuscularly every twelve hours, to be discontinued after two or three days and mild sedatives given orally; (5) tap water in small amounts as frequently as desired; (6) on the sixth or seventh day the addition of three small bland meals in addition to the milk and alkali mixture; (7) after ten to fourteen days six feedings daily of bland foods with the alkali mixture one hour after each feeding; (8) after ten days to a few weeks gastric analysis and X-ray examination; (9) transfusion when needed for shock; (10) when indicated five grains of desiccated ferrous sulphate three times daily for secondary anemia (which may result since blood regeneration may be delayed as a result of imperfect utilization of the dietary iron when the free hydrochloric acid is continuously neutralized) and (11) enemas rather than cathartics to eliminate putrified blood from the intestinal tract.

J. Duffy Hancock, Louisville.

MEDLAR, E. M. AND BLATHERWICK, N. R., WITH THE ASSISTANCE OF CONNOLLY, J. M., BRADSHAW, P. J. AND SAWYER, S. D.

The Pathogenesis of Dietary Nephritis in the Rat. Amer. Jour. Path., 13:6-881, Nov., 1937.

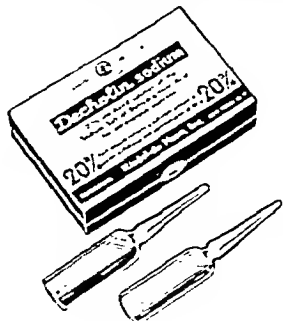
At the present time bacterial toxins and parenterally introduced proteins (nephrotoxins) are considered of greater etiological importance in diffuse degenerative changes in the kidney than are dietary factors. With this statement in the fore the authors detail their experimental studies on the production of degenerative nephritis in the rat when fed diets containing a large but varying percentage of protein. Rats with one kidney removed developed extensive nephritis more rapidly than intact rats. Likewise when desiccated thyroid was added to the diet nephritis developed more quickly. Thus a diet containing 0.4 per cent thyroid fed to 3 rats developed a fatal nephritis in 148 days, whereas 9 rats on a diet containing 0.1 per cent of thyroid lived an average of 539 days. Nephrectomized female rats on a diet containing 75 parts of dried beef liver also developed extensive renal damage in a relatively short time. This series of rats was studied in an attempt to recognize the progressive phases of

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renal damage and led to the following observations.

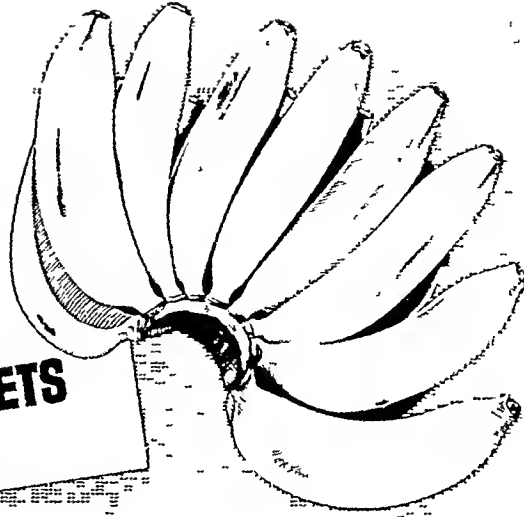
The primary renal lesion appeared to be a damage to the filter bed of the glomerulus. Just how was not clear. The endothelium, epithelium and basement membrane were all involved. The primary damage was focal in nature with progressive focal lesions developing, thus presenting lesions of different ages in a single glomerulus. In time the large majority of the glomeruli become sclerosed. Focal areas of necrosis and hyperplasia of the epithelial cells and an increase of the basement membrane occur in the tubules distant from the intertubular blood vessels, a fact which led them to believe that these changes had resulted from the presence of substances passing through the altered glomerular filter bed. The early injury to the tubular epithelium led to necrosis of only a few individual cells but to a considerable hyperplasia of the epithelium. This state was followed later by necrosis and dissolution of the hyperplastic tissue. The authors deemed it possible to attribute these changes to a functional selectivity of the cells.

The alteration in the basement membrane of the tubules depended apparently upon the passage of substances through the epithelial covering. The process was progressive in nature in those areas where the tubular epithelium was involved, namely, in the glomerular capsules, the loops of Henle, and the distal convoluted tubule. The general distortion of the kidney architecture in advanced cases appeared related to the extent and degree of increase of basement membrane material. This seemed to be the cause of the interstitial fibrosis. Acute inflammation was nowhere seen. In the later stages lymphocytic infiltration was common in the interstitial tissue. Spontaneous infection did not appear to be significant in the series. The nephritis related to the given diets, was a progressive degenerative disease. The final picture simulated so-called arteriosclerotic nephritis in man with the arteries or arterioles remaining normal. The histologic picture in advanced stages in these kidneys was quite similar to comparable stages of nephritis in rats produced by "nephrotoxins."

The authors conclude that the etiological factors capable of causing progressive degenerative nephritis are probably multiple and may be quite diverse in character. It is also conceivable that the final pathological picture is the same regardless of the provocative agent. They suggest that progressive degenerative nephritis depends upon an irreparable damage to the filter bed of the glomerulus. It may be the toxic products of an infection, so-called nephrotoxins, abnormal metabolic products, or (at least experimentally) certain diets that initiate the process.

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THORNTON, JOHN W.

The Relation of Gall Bladder Disease to Certain Heart Conditions. Jour. Iowa State Med. Society, 27:573-577, Nov., 1937.

The author discusses the relationship of gall bladder disease and certain types of heart disease, such as angina pectoris and coronary disease, as regards etiology, symptoms, differential diagnosis, and treatment. Gall bladder disease may not be listed as one of the actual causes of heart disease but there is abundant evidence that it exerts a harmful effect on the heart already damaged. In the diagnosis it is important to decide whether symptoms are due to the heart alone, the gall bladder alone, or to both combined. Surgical treatment of a diseased gall bladder may improve the heart condition by removing a focus of infection or other damaging factors. Where gall bladder pathology exists, surgery in many cases need not be denied because of complicating heart symptoms, and these symptoms may even be added justification for surgery.

Hanes M. Fowler, Fort Wayne.

SPRUNT, DOUGLAS H.

Simple Atrophy of the Liver—Its Relation to Increased Resistance. Arch. Path., 24:6738, Dec., 1937.

The author refers to recent experimental work of MacNider and of Smyth, Smyth and Carpenter, in which

certain morphologic changes from the normal is noted in the repair of renal and hepatic epithelium secondary to injury of these tissues. Hepatic epithelium as it regenerates is often found arranged in cords which do not run toward the central vein and are irregular in configuration. The cells are flattened and not polyhedral. The liver sinusoids are enlarged. There is no increase of connective tissue. This regenerated liver tissue is functionally effective, and has acquired distinct resistance to hepatotoxic agents, such as uranium nitrate, chloroform and carbon tetrachloride. This type of liver cell MacNider found also in 21 out of 92 senile dogs, and the livers of these dogs showed an acquired resistance to the action of chloroform—which control dogs did not possess.

The author calls attention to the similarity of these regenerated liver cells to those of simple, or brown, atrophy of the liver in man and suggests a relationship between simple atrophy and the body's resistance to toxic agents. With this thought in mind the author studied 387 livers from routine autopsies and found eleven which gave the morphologic picture described by MacNider. He postulates that these altered cells in human livers, similar to the altered cells in those of the dogs described which were found not to have lost their physiologic function and had become more resistant to toxic agents, may mean that persons with this type of liver may also be more resistant to these poisons, in which case atrophy assumes a new role in the phenomena of resistance and immunity.

N. W. Jones, Portland.

BRIDGES, M. A.

A Pre and Postoperative Nutritional Regimen. A Proposed Fire Point Schema. New York State J. Med., 37:2009, Dec. 1, 1937.

The author urges a definite routine in preparing patients for surgery. For five days before the operation, the diet should be low in fats and high in carbohydrates to minimize the danger of acidosis. As much as one-half pound of hard candy may be given daily. Leafy vegetables with high roughage content should be avoided because of the marked incidence of spastic colon. One heaping teaspoonful (45 grams) of common table salt, administered in capsules, is recommended daily to improve weight. Sedatives, particularly the barbiturates, are helpful; catharsis immediately before the operation is condemned.

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*J.A.M.A., Jan. 8, 1938; Ceder & Zom,
Pub. Health Rep., Nov. 5, 1937.

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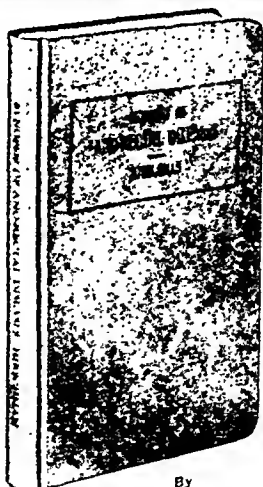
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BASIC OPERATIONS IN COMMERCIAL CANNING PROCEDURES

I. CLEANSING OPERATIONS

● As reference to a recent text on canning will disclose (1) the details of commercial canning procedures will vary from product to product. There are, however, certain basic operations which are included in practically all canning procedures. In the belief that they may prove of interest, it is our intention to describe in broad detail the nature and purposes of these essential operations.

One of the first and most important steps in commercial canning is the thorough cleansing of the raw food material received at the cannery. The purpose of such an operation is, of course, immediately evident, namely, to remove soil, dirt or other inedible substances which may be present. However, cleaning also serves to reduce substantially the load of spoilage bacteria with which Nature usually endows raw foods.

Commercially, cleansing is effected in a variety of ways. In general, however, water washers specifically designed for the various types of products are used. In these machines, the raw food material is subjected to high-pressure sprays or strong flowing streams of potable water while passing along a moving belt or while being tumbled by agitating or revolving screens. Sometimes a "flotation" type of washer is also used to remove chaff or similar material. With cer-

tain products, water washing is preceded by a "dry" cleaning treatment in which adhering soil and dirt is mechanically removed from the food by revolving or agitating screens, or by strong air-blasts.

Also, in certain canning procedures, operations whose basic functions are not primarily to clean the raw material may also exert a cleansing effect. Thus, the "blanch" or scalding treatment accorded many products serves to clean the food, as does the water spray sometimes applied to foods after the blanch.

Modern canners know the necessity of thorough cleansing of the raw materials they use. They appreciate that thorough cleansing and removal of extraneous material decreases the load of spoilage organisms which must be destroyed by the heat processes to which all canned foods are subjected. They also appreciate the necessity of maintaining strict plant and equipment sanitation to destroy spoilage bacteria which may be carried in by raw foods.

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(1) 1937 *Appertizing or The Art of Canning*, A. W. Dittine, The Trade Pressroom, San Francisco

(2) *Preventive Medicine and Hygiene*, M. J. Rosenau, Appleton-Century Co., New York.

This is the thirty-third in a series of monthly articles, which will summarize, for your convenience, the conclusions about canned foods which authorities in nutritional research have reached. We want to make this series valuable to you, and so we ask your help. Will you tell us on a post card addressed to the American Can Company, New York, N. Y., what phases of canned foods knowledge are of greatest interest to you? Your suggestions will determine the subject matter of future articles.



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New Bucketless Lead Weighted Gastro-duodenal Tube with a Review of the American Contribution to the Development of These Tubes

By

MOSES EINHORN, M.D.
NEW YORK, NEW YORK

BEFORE describing my tube, I should like to give a general summary of the various types of tubes and buckets used for duodenal intubation, commencing with the early pioneering days to the present time, so that we may observe the gradual development of these instruments, and emphasize the special features which each author claimed for his tube.

The earliest pioneer work of successfully intubating the duodenum was accomplished in 1895, by Hemmester (1) who was the first to describe a device (Fig. 1, A), consisting of a tube connected with an inflatable rubber balloon the shape of the stomach, grooved on its upper surface for the passage of another tube into the duodenum through the pylorus.

Hemmester's work was soon followed by that of Kuhn (2) who in 1898, devised an instrument (Fig. 1, B), consisting of a "very flexible thin steel spiral tube, which was pushed through a thin stomach tube." The spiral served to prevent too much bending and kinking and doubling upon itself under pressure.

There was no further development along this field until about eleven years thereafter, when Dr. Max Einhorn started to experiment with his bucket. To him should be given the major credit for the first attempt to scientifically study the physiology of the duodenum, the pancreas and the gall-tract by means of the duodenal tube.

Max Einhorn experimented a number of years on various tubes and buckets, and finally in 1909, developed his duodenal pump (3), which consisted of a gold-plated perforated metal capsule (Fig. 1, C), tied at the end of a thin rubber tube. The terminal capsule is 7/8 inches in length, 23 French in diameter, and 59 grains in weight, and can be unscrewed for cleansing purposes. The main purpose of his duodenal tube is to allow the stomach to do the work of pushing the tube through the pylorus.

A few months later, Gross (4) described another tube (Fig. 1, D), somewhat similar to Einhorn's except that it was larger in size, and had a multiperforated silver-plated leaden ball at its distal end, 5 8 inches in length and 160 grains in weight, covered by the tube on all sides. Gross facilitated the passage of the tube through the pylorus, first by gravity of the leaden ball, and second by placing the patient in various positions.

Jutte (5) in 1912, devised a small calibered duodenal tube (Fig. 1, E), which has a lead sinker at its distal end, 4 8 inches in length, 12 French in diameter, and 21 grains in weight, with numerous small openings in the soft rubber tube above it. A wire obturator which acts as a stilette assists in the passage of the tube.

Palefski (6) in 1914, described his bucket (Fig. 1, F), which consists of a globular gold-plated lead tip,

6/8 inches in length, 34 French in diameter, and 140 grains in weight, 1/2 of which is solid, serving as a weight, and the other half hollow and perforated, terminating with a neck to which the tube is attached by means of silk thread.

He stressed the importance of weight, and claimed also, that a perforated ball acts as a sieve allowing the aspiration of the liquid only, leaving behind the particles of food, thus preventing clogging of the tube.

Rehfuss (7) in 1914, introduced a tube (Fig. 1, G), with a slotted instead of a perforated tip. The tip, which is olive-shape, is one inch in length, 29 French in diameter, and 90-100 grains in weight, with four elongated slots on either side, so cut that the diameter is as great as the calibre of the rubber tubing.

Rehfuss claims that in this manner we are assured a more perfect aspiration of the rubber tubing. The weight is sufficient to assure rapid swallowing, at the same time assisting by gravity its passage through the pylorus and into the duodenum.

Kanavel (8) in 1916, described his new tube (Fig. 1, H). The bucket is of the same shape as the Rehfuss, except that the lumen of the exit is larger. It is attached to a tube which is 30 inches in length, and 10 French in diameter. Through this tube a carrier of piano wire is introduced. After the insertion of the tube, the wire is withdrawn and the proximal end of the tube is attached to another tube larger in size, by a screw lock.

Kanavel claims that the piano wire carrier assists in the introduction of the tube, particularly in cases of vomiting; also, that the larger exit of the bucket permits the stomach content to be aspirated with greater freedom.

Buekstein (9) in 1919, modified the duodenal tube in a few details. He endeavored to get rid of the metallic end piece, since he thought it possible that a metallic weight of that sort might, if left in contact with the soft living membrane of the duodenum or jejunum over a long period of time during a course of duodenal feeding, produce an erosion with possible hemorrhage or ulceration. He introduced a modification consisting of a light weight tip (Fig. 1, I), 5 8 inches in length, and 23 French in diameter, which could be fastened to the duodenal tube by catgut. After a few days, the catgut stitch would be absorbed and the tip would become detached from the tube and pass out through the intestines to be recovered in the stool.

Lyön (10) in 1920, described a new tip (Fig. 1, J), elongated pear-shape, 9 8 inches in length, 27 French in diameter and 70-90 grains in weight, with four slotted openings on the sides, and a round perforation at its end. The tip is ground down to a tapering proximal end of the same calibre as that of the rubber

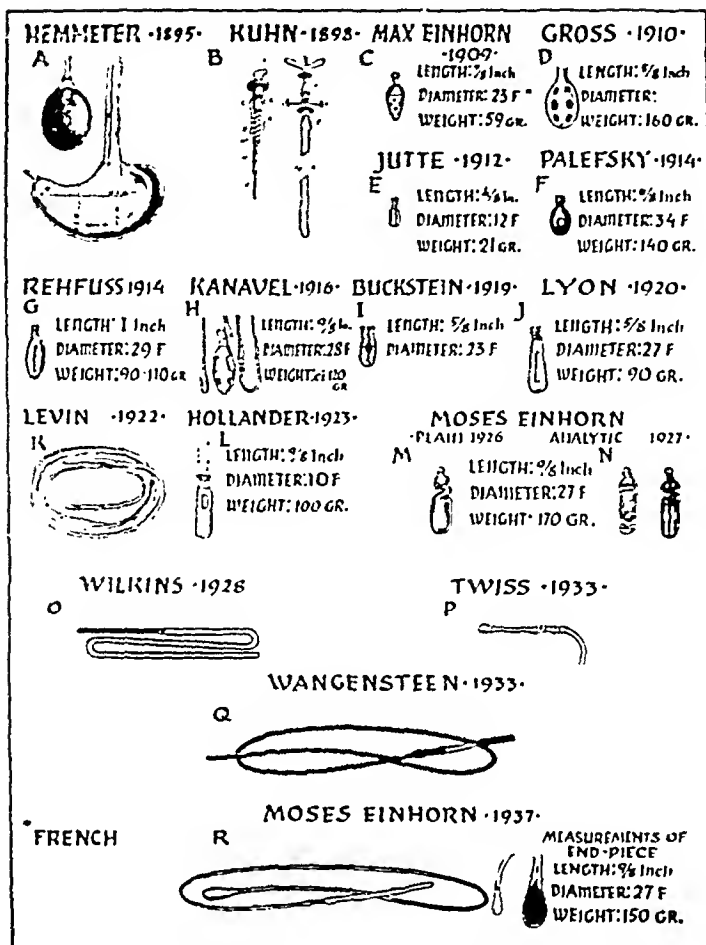


Fig. 1. New bucketless lead weighted gastro-duodenal tube with a review of the American contribution to the development of these tubes.

tube. Its shank is elongated and serrated, thereby doing away with the necessity of tying in the tip with surgeons' silk.

Lyon also emphasized the desirability of weight, and called attention to the difficulty which is encountered when the tube is withdrawn from the duodenal zone into the stomach, and more especially when it passes the pylorus on its upward journey, on account of the shoulder or collar on the proximal side of the olive and ball type tips. By having the neck tapered and narrow, this difficulty is eliminated.

Levin (11) in 1921, advocated the use of a tipless gastro-duodenal catheter (Fig. 1, K), which he preferred to introduce through the nose. It has a velvet edge at its terminal end exactly like a urethral catheter, 14 or 16 French in diameter, and side openings which are oval in shape.

Levin claims that by introducing the tube through the nasal route there is no tickling of the soft palate, the patient does not experience any discomfort or choking sensation, and it is easier to withdraw the tube, as there is no metal bucket at the end.

Hollander (12) in 1923, described his narrow tip

(Fig. 1, L), which is 9/8 inches in length, 10 French in diameter and about 100 grains in weight. There are four elongated fenestrae occupying about 1/3 of the length of the tip, situated at its upper portion. The lower part is solid lead filled shell, weighing 70 grains.

Hollander emphasizes the importance of weight, the lower part heavier than the upper part, and claims that a narrow tip can pass into the duodenum more readily than a wider one.

In 1926, I described my spiral bucket (13) (Fig. 1, M), which is 9/8 inches in length, 27 French in diameter, and 170 grains in weight. It is of capsule shape with an obtuse point, and has three divisions: (a) the top, made of nickel, through which a large opening is bored, which serves as an outlet for the drainage chamber to the tube, which is attached to the neck of the capsule (b) the spiral made of round metal wire, which connects the top to the body, and by its circular arrangement offers a large drainage area (c) the bottom, made of solid lead, and connected with the top by the spiral.

I also stressed the importance of weight, particu-

EINHORN—NEW BUCKETLESS LEAD WEIGHTED GASTRO-DUODENAL

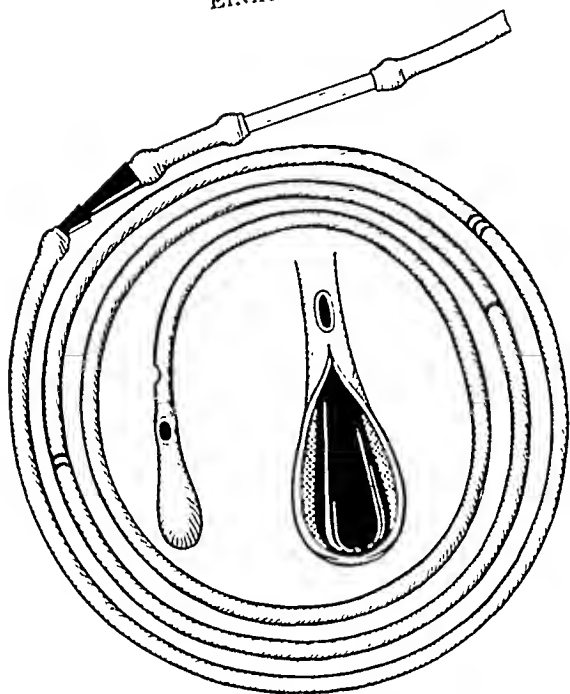


Fig. 2. New bucketless lead weighted gastro-duodenal tube.

larly its proper arrangement, the distal end being three times heavier than the upper part, which aids it to travel along the small curvature and keeps it in proper place in its progress toward the pyloric opening.

In 1927, I described my analytic bucket (14) (Fig. 1, N), which is based on the same principle as the spiral bucket, but the lower part is constructed so that a space is left between the central column and the outer shell. It is in this space that the different paper strips prepared with Toepfer's solution, phenolphthalein, blue litmus and benzidine are inserted. There are four openings or fenestrae in the outer shell, so that fluids may take effect on the last strips. The bottom of the central column is so threaded that the bottom of the bucket may be screwed to it. The analysis of the gastric content is then made according to the change in the color of the paper strips.

Wilkins (15) in 1928 described his tipless mercury weighted stomach tube (Fig. 1, O). The tube is made of soft flexible rubber throughout, and measures 46 inches in length. It has a mercury compartment, $4\frac{1}{2}$ inches in length and $\frac{3}{16}$ inches in diameter at its lower end, as a result of which the tube at its end is very heavy. The openings in the tube are situated above the mercury compartment.

Wilkins emphasizes the importance of weight, and the fact that there is no metal about the tube which can injure the membrane of the stomach or duodenum, or become detached as the metal tips of tubes in common use can do.

Twiss (16) in March, 1933, described his new tube (Fig. 1, P), which consists of a small sized bucket with concave slots. A calibrated tube is attached to the proximal end of the bucket, and at its distal end is a swivel which is connected to a small solid terminal ball by rubber tubing of smaller size.

Twiss claims that the concavity of the slots will prevent adherence to the surrounding viscera and allow a free flow of fluid, and that the use of a swivel joint, prevents as far as possible, looping of the tube in the stomach; also, that this particular arrangement allows the concentrated weight of the tip to act as a leader in drawing the bucket through the pylorus into the duodenum, and also as an anchor in retaining it there.

Wangensteen (17) in 1933, stated that following abdominal operations, a paresis of the intestines of varying degree is the rule, and usually results in intestinal distention. He found from observation that a simple duodenal tube placed in the stomach does not keep the viscera continuously empty and so he developed a type of tube which he claims to give good results.

The tube (Fig. 1, Q) is 50 inches in length, weighted at its tip, and is processed for four inches at its terminal end to appear opaque for fluoroscopic examinations. There are nine openings which extend upward ten inches from the end of the tube.

Wangensteen believes that while the tube is in the duodenum, drainage is accomplished for the duodenum and the stomach at the same time. This is true if all the openings are below the fluid level, but in the event that one of the upper openings is above the fluid level, then syphonage will stop, and the rest of the fluid will be retained.

Ryle (18) described a tube which he weighted at the end with an oval shape lead piece covered with rubber on all sides.

From the description of the various tubes and tips given above, and from the advantages emphasized by each of their authors, we can summarize the salient points as follows:

1. The weight of the tip is an important feature in its construction.
2. The distribution of the weight, with the lower part three times heavier than the upper part is essential.
3. To eliminate injurious effects of the metal tip it is necessary that it be silver or gold-plated or covered with a layer of rubber.
4. The top of the bucket should be tapered and narrow and about the same size as the tube in order to remove the difficulty encountered at the glottis upon removing the tube.
5. It is desirable to have the openings in the tube, instead of the bucket, as the rubber margins prevent the cutting of the mucous membrane upon suction.
6. The openings should be slotted and smaller than the lumen of the tube, to prevent clogging by particles of food.
7. Tying of the neck of the bucket should be eliminated, as the rough edge of the knot may irritate the mucous membrane.
8. The tube should be so constructed that its openings or fenestrae do not lie flat on the visceral wall, but are raised to permit a continuous flow or drainage.
9. The bucket and tube should be constructed in one unit, to eliminate the possibility of its becoming detached, which is usually feared by the patient.
10. An increased number of openings extending along the lower end of the tube does not tend to increase the flow, but on the contrary, if one of the

upper openings is above the level of the fluid, syphonage will cease, and the rest of the fluid will be retained.

11. Catheter type tubes are satisfactory for introduction through the nasal route, but in gastric and duodenal intubation a tube with a tip is more serviceable.

Taking all these points into consideration, I gradually developed a tube, which in my opinion, embodies all the positive features mentioned above. For a long time I experimented with my tube in order to convince myself of its merits, and now I am ready to present it to the medical profession as an ideal tube for gastric and duodenal intubation.

The tube (Fig. 1, R), is 50 inches in length, and 14 French in diameter, and is semi-soft in consistency, flexible and of good resiliency. Its terminal end encases an elongated drop-shape lead sinker (Fig. 2) narrow and tapered above, but increasing in size at the bottom. The size of the terminal portion of the tube, including the sinker with its layer of rubber is 150 grains in weight, 9/8 inches in length, and 27 French in diameter at the bottom, while at the top, it is the same size as the tube. Two openings slotted in appearance are situated just above the sinker, 1/2 inch apart, on opposite sides of the tube. The diameter of the slots is smaller than the lumen of the tube, thus preventing clogging of the tube by particles of food. The small space between the sinker and the first perforation is filled with rubber.

Upon looking over the literature, I found quite a variation of the markings on the tube. Therefore, to ascertain the exact position of the markings, I fluoroscoped a number of patients after they had swallowed my tube, and I measured the distance from the lips to the cardia. Also, X-ray films were taken after a barium meal, and measurements from the cardia to the pylorus were obtained.

I thus arrived at the average readings for my tube, and placed one mark at 47 cm. or 17 inches from the end of the tube, which represents the distance from the lips to the cardia; two marks at 28 inches, which represents the distance from the mouth to the pylorus, and three marks at 32 inches. However, the physician's

judgment should always determine the amount of tubing for each individual, and he should not rely entirely on the markings.

Advantages:

1. The fear that the patient usually experiences as regards the possibility of the metal bucket becoming detached is eliminated, as the lead dropper is encased in the tube.

2. Swallowing of the tube is accelerated because of the weight of the dropper, which is sufficient to permit its passage through the esophagus with no discomfort to the patient.

3. The tube maintains its intended course along the stomach pathway because of its weight which is 150 grains, its proper arrangement, the lead sinker being so constructed that the lower part is 3 times heavier than the upper part which aids it in travelling along the small curvature and keeps it in the proper place in its progress through the pyloric opening.

4. There is no likelihood of regurgitation of the bucket from the duodenum into the stomach, as is usually the case with other tips, because of the special distribution of the weight of the sinker, which anchors the tube securely in the duodenum.

5. No discomfort is encountered at the glottis upon the removal of the tube, because of its tapered shape and the gradual decrease in size at the neck.

6. There is no need for silver or gold-plating the metal bucket to avoid impairing the mucous membrane, as the sinker is encased in rubber.

7. The openings of the tube have rubber margins, and there is no possibility of cutting the mucous membrane upon suction, as is usual with metal buckets.

8. The openings are slotted, elongated and smaller in diameter than the lumen, and offer a large drainage area, at the same time preventing clogging of the tube with particles of food.

9. A continuous flow is offered through the openings, due to the special arrangement of its lower end, the sinker being 27 French in diameter, while the tube is only 12 French, thus forming an arc which prevents its adherence to the visceral wall.

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The Gastric 'Relief' in Duodenal Ulcer: An Accessory Aid in Diagnosis

By

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ALTHOUGH Holzknacht (1) and others observed the appearance of the gastric mucosa, incidental to the roentgenologic study of the stomach, it was not until von Elischer (2) that a definite effort was made by a specific technique to roentgenologically demonstrate the rugal folds of the stomach.

The method he recommended consisted of the administration of 75 grams of zirconium oxide with 30-40 c.c. mucilage gum arabic. About 30-40 c.c. of this emulsion was given to an individual on an empty

tion of Forsell in 1913 (3). In this work, he first brought to our attention his conception of the changing nature of the gastric mucosa as conditioned by the intrinsic motor function of the muscularis mucosa. This idea has been elaborated by him in many important contributions which followed.

Schwarz (4) in 1916 showed the importance of a study of the gastric rugae in chronic gastritis, by demonstrating that the prominences in the roentgen picture of the stomach corresponded to swollen hyper-

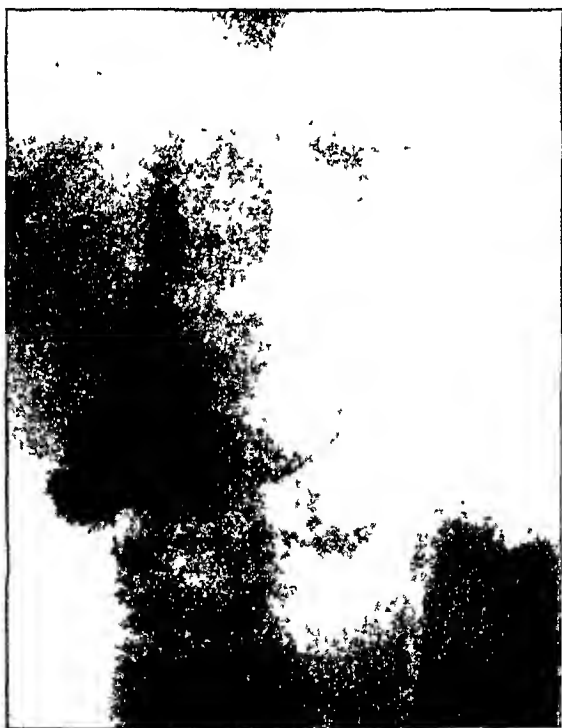


Fig. 1. A normal 'relief picture' of the gastric mucosa.

stomach by means of a stomach tube. A moderate amount of air was then introduced. The patient was then alternately placed in a horizontal and lateral position in order to produce a uniform distribution of the emulsion over the internal surface of the stomach, thereby bringing out the fine detail of the mucosal folds. After a few minutes the patient was studied roentgenologically, the examination being repeated two or three times at intervals of a few minutes.

Further impetus was given to the roentgenologic study of the gastric mucosa by the classical contribu-



Fig. 2. The gastric 'relief' in a case of duodenal ulcer. Note the exaggerated prominence of the rugal fold.

emic folds of mucosa protruding into the lumen of the stomach.

Eisler and Lenk (5) were able to successfully study the gastric rugae by employing an aqueous suspension of barium which they distributed by palpation over the stomach, and were apparently the first to describe the phenomenon of the radiating convergence of mucosal folds at the site of the niche of a peptic ulcer.

From the standpoint of technical advance in the roentgenological study of the mucous membrane, we are indebted to the work of Akerlund (6) and Berg-

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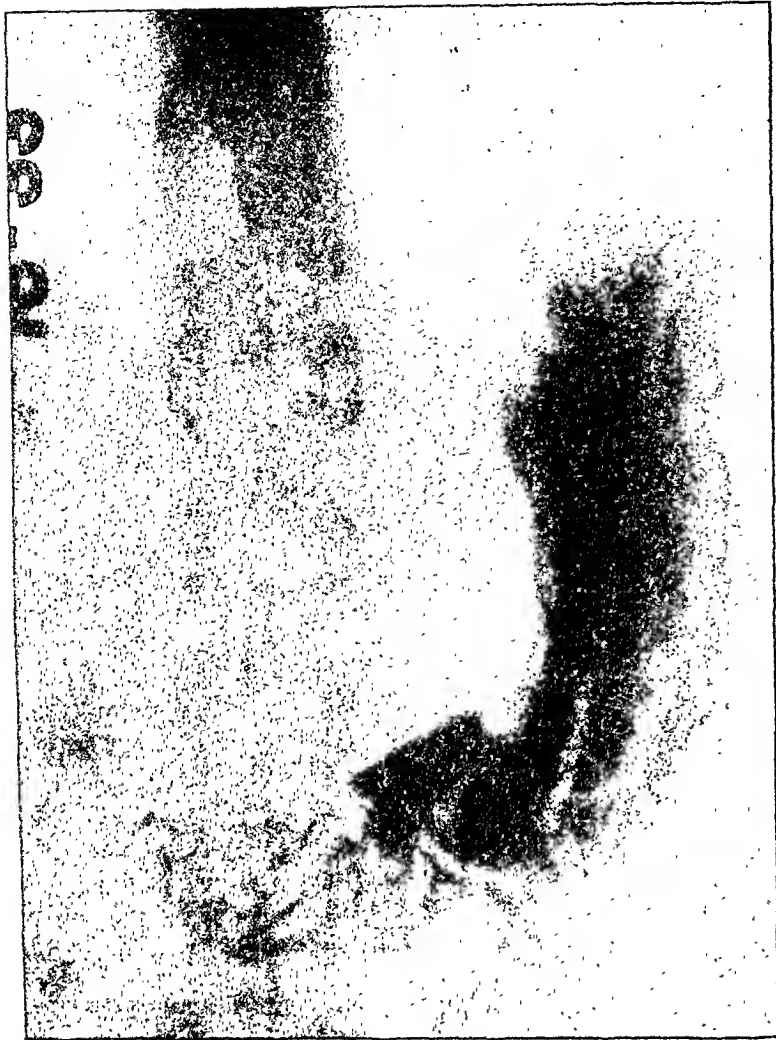


Fig. 3. Another example of thickening and tortuosity of the rugal folds of the stomach in a case of duodenal ulcer.

mann (7) who by popularizing the method of graded compression, brought more clearly to our attention the variations in the roentgen appearance of the mucosal structure in health and disease.

Rendich (8) in this country did pioneer work in emphasizing the importance of specific attempts to bring the gastric mucosa into clear relief for more detailed study.

The value of the roentgen demonstration of changes produced by chronic gastritis has been verified by Gutzeit (9), Velde (10), Baensch (11), Chaoul (12), Hecker and Prevot (13), and Cole (14).

Pathologically the relation of inflammatory gastric changes to ulcer had been recognized by Cruveilhier. In 1897, Nauwerk (15) claimed that chronic gastritis played an etiological role in ulcer. Similarly Konjetzny (16), Kalima (17), Puhl (18), and others have demonstrated the existence of inflammatory mucosal changes in relation to peptic ulcer.

Faber (19) in the Schorstein lecture delivered at the London Hospital Medical College on May 20, 1927, stated, "We realize then, that the very oldest hypothesis advanced by Cruveilhier, is once more coming in the front—that it is in the gastritis we must seek the origin of the chronic ulcer. Gastritis is likely to assume that predominant position in the pathology of the stomach which has been assigned to it from time to time in the past, only to be subordinated to the theory of nervous, functional disturbance and chronic simple ulcer."

Anderson (20) showed the close clinical and path-

ological relationship of gastro-duodenitis to ulcer, and called attention to the value of the roentgen method of demonstrating its presence.

Thus there appears to be not only a close relationship between peptic ulcer and pathologic evidence of chronic gastritis at least in some cases, but in addition there is substantial and apparently reliable evidence to justify the assumption that such inflammatory changes may frequently be recognized in the roentgenogram.

It is surprising with what frequency one may recognize roentgenologic evidence of thickening and distortion of the mucosal folds in cases of peptic ulcer. Even where the lesion is a post-pyloric (duodenal) ulcer swollen tortuous gastric folds showing marked deviation from the normal may be readily demonstrated. So frequent in fact is this association, that it has been possible in many cases to predict from the roentgenologic appearance of the gastric mucosa that a duodenal ulcer would be discovered. In borderline cases where the direct evidence of ulcer was not altogether definite, we have learned to consider a characteristic gastric 'relief' as strong presumptive evidence of the existence of ulcer. Where the question of the advisability of further check-up study has arisen, we have been definitely influenced in its favor, by such roentgen evidence of thickening and distortion of the rugal folds of the stomach. Because of this close association of peptic ulcer and the characteristic mucosal relief picture, we believe that this finding may be justifiably considered as important 'indirect' evidence in establishing the diagnosis of peptic ulcer. A similar gastric appearance may to be sure,

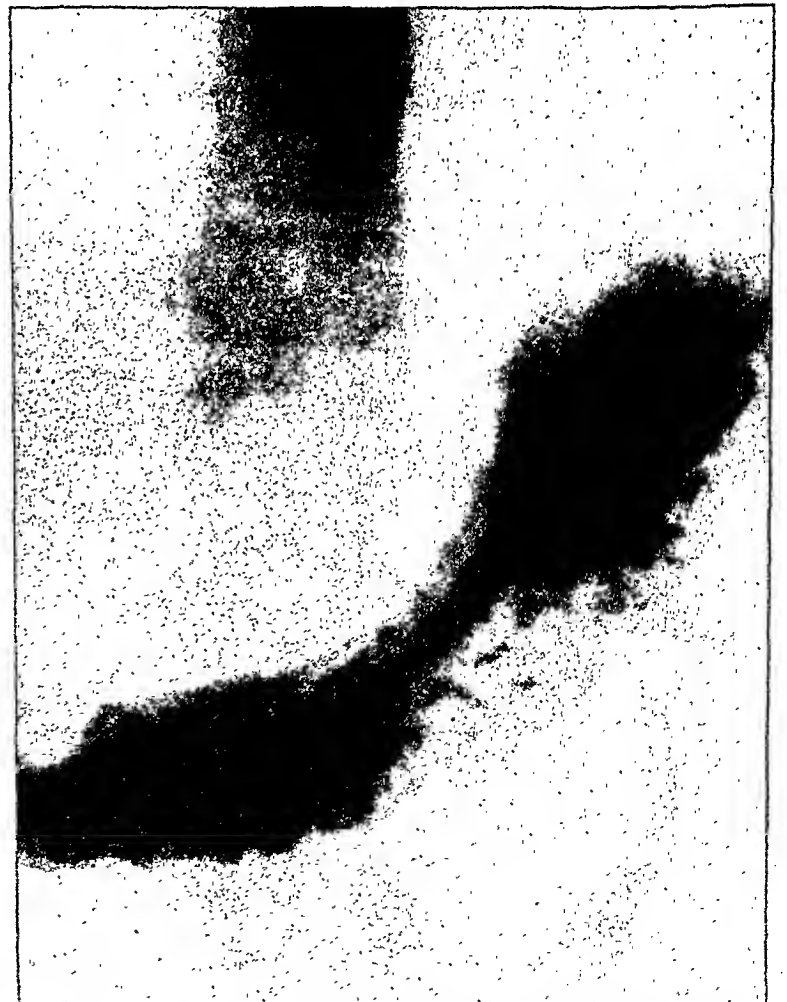


Fig. 4. Tortuous and prominent mucosal folds of the stomach associated with duodenal ulcer.

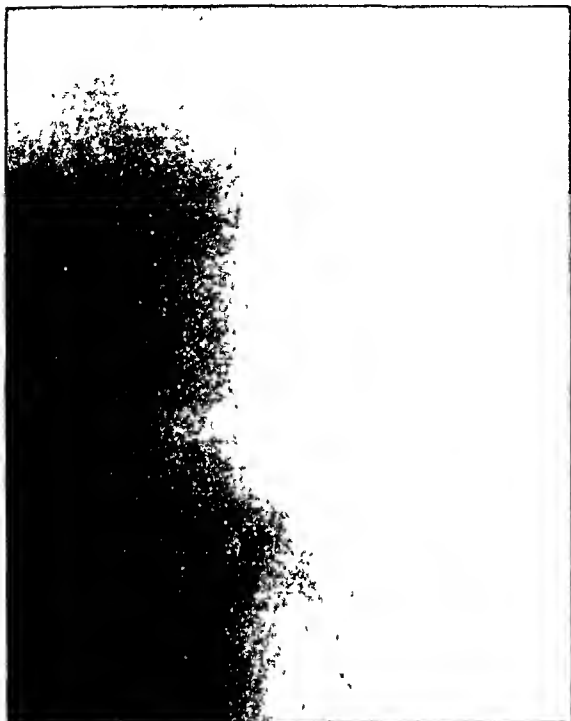


Fig. 5. Tortuous and prominent mucosal folds of the stomach associated with duodenal ulcer.

be found in the absence of any of the direct manifestations of ulcer, and apparently as the roentgen counterpart of a chronic gastritis without ulcer. In many cases, however, roentgen evidence of an ulcer has been found in association with this gastric relief.

The causal relationship of the roentgen appearance of the gastric mucosa and the presence of ulcer, particularly duodenal, is not altogether clear. In some cases perhaps there is an actual gastritis which provides fertile soil for the development of ulcer. On the other hand the presence of a peptic lesion may possibly secondarily lead to oedema and swelling of the gastric folds. Whatever the etiological relationship may be, their close association is both interesting and important.

In studying the mucosal relief we have used a simple mixture of barium and water in approximately equal amounts. We feel that the more aqueous the solution the greater the opportunity for its entering all the recesses in a homogeneous manner. The suspension is spread over the mucosa manually. Films are taken in the prone position and a number of exposures are made. These are developed immediately, and further films are taken if necessary. No compression apparatus is employed. While the beauty and diagnostic value of many of the films obtained by special compression technique are unquestioned, it is at best a time consuming procedure. In an institution such as Bellevue Hospital where as many as thirty to forty new stomach cases may be radiographed in a single afternoon, so time consuming a procedure as the technique of graded compression is hardly practical. Even if each examination took only fifteen minutes, eight to ten hours of continuous labor would

be required without cessation or any form of interruption. Moreover it is our experience that even where suspicion on fluoroscopic examination may center on a single area, it may not be safe to neglect the taking of films of the rest of the stomach and duodenum. It is not unjustifiable to state, I believe, that even the most experienced and skillful fluoroscopist may at times fail to note a lesion which he later recognizes in the films. Presumably then, the ideal technique of taking small films of various areas with graded compression under fluoroscopic control, should theoretically include every part of the stomach and duodenum. By centering on one area to the exclusion of others, a lesion may occasionally be overlooked in the region that is not specifically under observation. To make a study of such ideal nature would considerably increase the time required. In addition the amount of exposure to the operator would be enormous.

The routine procedure as employed at Bellevue Hospital is as follows. Under fluoroscopic control the patient swallows a mouthful of a suspension of equal parts of barium and water. The gastro-duodenal mucosa is 'whitewashed' with this mixture. More of the suspension is administered depending on the amount required to visualize the mucosa with manual compression. Films may then be taken in the prone position. Or if a contour study of the stomach and duodenum is made after the more liberal administration of the barium suspension, then in addition to immediate films, a film may be taken every ten minutes as the stomach empties. Such films may be developed promptly to determine the appearance of the gastro-duodenal mucosa during the course of the examination. The Bucky diaphragm may be used to advantage in bringing out the finer detail of mucosal structure.

The fluoroscopic examinations are made in one room, and each patient on completion of this study passes through a revolving door into the next room where films are taken by a technician. Details as to the position of the patient and the number of films desired are put down on a sheet on which are recorded the findings of the fluoroscopist, who may uninterruptedly continue the examination of his many patients. Not only is such a procedure necessitated by the practical problem of examining large numbers of patients in a comparatively short time, but it is



Fig. 6. Gastric relief showing prominent moderately tortuous rugal folds in a case of duodenal ulcer.

very doubtful if the accuracy of the results suffers from the failure to employ the technique of graded compression. Careful fluoroscopy with manual palpation to visualize the gastro-duodenal mucosa, as many films in various positions as may be deemed essential, a detailed comparison of the fluoroscopic and radiographic findings after the films have been developed, and a liberal use of check-up examinations where the slightest failure of complete correlation arises, all combine to reduce the possibility of error.

Whatever may be said in favor of the method of graded compression when used in a small institution with only a few cases a day, there are serious objections to its routine employment in a large institution.

There is also the possibility that the roentgen appearance of the gastro-duodenal mucosa obtained without artificial compression may more nearly approach its real structural nature. It is not at all unlikely that compression under certain conditions par-

ticularly in the hands of the less skilled may produce at times an appearance of puckering which is entirely artificial and at other times produce an obliteration of normal markings by compression even moderately in excess of the optimum.

Examples are included of the thickened tortuous rugal folds so frequently found with duodenal ulcer, as obtained by the simple technique as described above.

SUMMARY

1. A historical survey is presented of the subject of the roentgen demonstration of the gastric mucosa.

2. A simple technique is described for the demonstration of the gastric mucosa particularly applicable to the examination of large numbers of patients.

3. Thickening and tortuosity of the mucosal folds is a common finding in association with duodenal ulcer and may be considered as an accessory diagnostic aid.

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Effect of Introducing Oxygen into the Isolated Colon of a Patient with Chronic Ulcerative Colitis*

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IN 1931 Felsen (1) reported that the repeated introduction of oxygen into the colon was of definite value in the treatment of chronic ulcerative colitis. This observation was confirmed by Golob (2) who recorded a case of chronic ulcerative colitis following amebiasis in which a spectacular improvement followed a course of colonic oxygenation. These observations appeared to us to have a special significance in view of our finding of the almost constant association of *Bacterium necrophorum* with cases of chronic ulcerative colitis in man and the exceeding sensitivity of this organism to oxygen (3).

During the past year Fry and one of us (4) found

that the insufflation of oxygen into the isolated colon of a normal dog into which a human strain of *Bacterium necrophorum* had been introduced caused the rapid disappearance of this organism. In view of this result and because of the favorable reports of Felsen and Golob it seemed advisable to us to determine the effect of the introduction of oxygen into the colon on *Bacterium necrophorum* naturally occurring in cases of chronic ulcerative colitis. In a previous study we have reported that the establishment of an end-ileostomy in patients with chronic ulcerative colitis leads to a simplification of the colonic flora, the exogenous bacteria accompanying the fecal stream disappear, and there develops a predominance of anaerobic organisms, of which *Bacterium necrophorum* has been found

* (From the Departments of Hygiene and Bacteriology and Surgery, The University of Chicago). This study was aided by a grant from the American Medical Association. Submitted August 13, 1937.

to be the most common (5). In our somewhat limited experience end-ileostomy was found to produce considerable clinical improvement, but in no case did the diseased colon become entirely healed. Recurring exacerbations of the disease were observed from time to time with proctoscopic evidence of alternating healing and recurrence of the typical lesions and these were associated with the disappearance and reappearance of *Bacterium necrophorum*.

The patient observed in this study has been referred to as Mrs. N. or Patient No. 1 in a previous report (6). This was a case of typical severe chronic ulcerative colitis on whom an end-ileostomy was performed in April, 1933. Following the operation the patient improved decidedly and gained considerable weight. One year later she gave birth to a normal healthy child. During the period of pregnancy the physical condition of the patient was much improved and proctoscopic examination disclosed also a comparable improvement in the colon. Following delivery the diseased process became worse and since this time there have been alternating periods of improvement and recurrence. On January 29, 1937, she was admitted to the hospital for the present study. At this time the process was quite active and the patient stated that the colon discharges, which numbered 6 to 8 per day, were blood-tinged and contained considerable mucus. Oxygen was introduced into the isolated colon through a long sterilized rubber catheter which was inserted into the rectum for a distance of about 30 cm. The oxygen was obtained from a large tank equipped with a metal valve control. The gas was bubbled through water in order to estimate the volume used. A manometer was attached by means of a side arm to the gas line to prevent the pressure from exceeding 4 or 5 mm. of mercury.

Treatment by means of this oxygen insufflation was begun on February 5th and continued to May 27th, a period of 112 days. During this time the patient received oxygen insufflation on 78 days and no treatment on 34 days. The length of each treatment varied from 2 to 12 hours. Altogether oxygen insufflation into the colon was administered for 460 hours with no interval between treatments exceeding 4 days. The patient was ambulatory except for the period of the oxygen insufflation. During the course of the treatment her general condition improved and there was some increase in weight. Weekly proctoscopic examinations during the entire period revealed alternating improvement and exacerbation of the diseased process. Cultures were taken from the colon three times each week, once from the bowel wall at the time of the proctoscopic examination and twice from discharges collected through a sterile rubber tube inserted into the rectum. In all 43 bacteriological examinations were made. Eosin methylene blue plates and blood agar plates were streaked with the specimens. The eosin methylene blue plates were incubated aerobically for 24 hours at 37 degrees Centigrade. When the colon discharges were bloody there was often no growth on these aerobic plates. During short periods of improvement large numbers of *Proteus* colonies appeared. At no time were typhoid, salmonella, or dysentery bacilli detected. Aerobic and anaerobic blood agar plates were streaked at the same time and the anaerobic plates were incubated under conditions which have been previously described (7). Although the colon was

entirely isolated its bacterial flora varied considerably from time to time. *Bacterium necrophorum* was found in 27 of 43 examinations and was the predominant organism 8 times. It was almost invariably found in large numbers whenever the diseased bowel became worse and more blood appeared in the rectal discharges. A small black colony was often seen on the anaerobic blood agar plates. This colony was encountered in 23 of 43 examinations and on 7 occasions it was the predominant organism. It proved to be a coccus and has frequently been observed in the examination of normal stools. In 18 of the 43 examinations there appeared on the anaerobic blood agar plates colonies which displayed a green zone of hemolysis. These were for the most part Gram-negative cocci, although some were Gram-variable. A smooth white non-hemolytic colony was also found on the aerobic and anaerobic blood agar plates. This was a Gram-negative rod, was found 28 times, and proved to be the predominant organism on 10 examinations. It was representative of the colon group of the Gram-negative bacteria.

Since insufflation of the colon with oxygen failed to improve the diseased intestine and likewise failed to free it from *Bacterium necrophorum*, the question arose as to whether such treatment might give rise to strains of *Bacterium necrophorum* which were resistant to oxygen. This hypothesis was tested by exposing 7 pure cultures of *Bacterium necrophorum* to atmospheric oxygen and subsequently testing their viability. The strains used were isolated from the diseased colon at wide intervals during the course of the oxygen therapy. They were streaked on duplicate blood agar plates and incubated for 4 days under anaerobic conditions. Following incubation the plates were exposed to the air. At 30-minute intervals four colonies were picked and placed into freshly boiled and cooled Rosenow's dextrose brain medium to test for viability. The test was continued for a period of five hours. Growth regularly occurred in cultures exposed to the air up to 1½ hours and irregularly in some of the tubes up to 3 hours, but from 3 hours on to the end of the test period no growth was observed. There was no evidence that strains isolated during the later part of the oxygen treatment were more resistant to oxygen than strains isolated before the treatment was instituted.

DISCUSSION

The significance of *Bacterium necrophorum* in chronic ulcerative colitis remains difficult to evaluate. Further study has always revealed the presence of this organism in the colon in typical cases of the disease, but we have been unable to reproduce the process in experimental animals with pure cultures of *Bacterium necrophorum*. The long continued insufflation of oxygen into the colon in this patient did not bring about the improvement reported by some other observers. Nor did the treatment cause a disappearance of *Bacterium necrophorum* or greatly decrease the number of these organisms. The fact that *Bacterium necrophorum* introduced into the normal colon of the dog is readily destroyed by oxygen insufflation indicates that in the diseased bowel there must be a protective mechanism operating. This persistence is apparently not due to the development of a tolerance to oxygen, but may depend upon the presence of the organism in the deeper layers of the intestinal wall.

It should be emphasized, however, that the failure of colonic oxygenation in this one chronic case should not discourage further trial of the treatment, which may be more effective in the early and more acute phases of the disease.

SUMMARY

Oxygen gas was repeatedly insufflated into the isolated colon of a patient with severe chronic ulcerative colitis. The treatment was given for periods varying from 2 to 12 hours over a time interval of 112 days. During this time 43 bacteriological examinations were made of the colon and its discharges. The isolated dis-

eased colon failed to heal and *Bacterium necrophorum* continued present and was found in abundance, especially during periods when the diseased process appeared aggravated.

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The Effect of Orange Juice on Gastric Acidity*

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THIS short communication, based as it is on but a limited number of experiments, obviously cannot be regarded as settling anything, but the results of the work were so clear-cut and so according to what any chemist would have expected, that I believe the paper well warrants publication and also attention from gastro-enterologists everywhere. So far as I know it is the only answer we have to a question the great importance of which is just now becoming apparent. The paper will serve well if only it stimulates other investigators to confirm or disprove the conclusions now reached. Naturally the final answer to the question must come from studying the changes in the pH following the giving of fruit juices to many patients with ulcer.

W. C. A.

Opinions among gastro-enterologists differ as to the advisability of including orange juice in the diet of patients who have peptic ulcer. Some withhold it because they fear that it will increase the acidity of the gastric content; some doubt if it contains enough acid to do any harm, while others feel that it is so important to supply vitamin C to patients who are to live for some time on little besides milk that if there is any doubt about the matter it would be best to err on the side of giving fruit juices. Recently Rivers and Carlson and Alvarez and others have pointed out that patients who for a long time are on a strict ulcer diet are likely to have less than the minimal requirement of vitamin C in the blood, and it may well be that incipient scurvy sometimes accounts for the tendency to hematemesis seen in cases of peptic ulcer.

In order to determine the effects of orange juice on the pH of gastric juice, the following investigations were made. Orange juice was prepared freshly each

day. It was filtered and the pH was determined with a glass electrode in an amplified system. The apparatus and its use have been described by Dill, Daly and Forbes. The pH was chosen for study because peptic activity depends on the hydrogen ion concentration and not on the "free acidity." The latter is a vague term which does not mean much to a chemist.

The pH of the six samples of mixed orange juice (from several oranges) used in these investigations varied from 3.63 to 3.99. The oranges used by Kugel-mass in his study must have been more sour than those used in our work, since the juice from them had a pH ranging about 3.0. Kugelmass found that orange juice contains only small amounts of free acid, and that it is really a buffer solution made up mainly of the primary, secondary and tertiary salts of citric acid.

Gastric juice was obtained from patients one hour after they had taken an Ewald type of meal consisting of six arrowroot cookies and 400 c.c. of water. Table I shows that the pH of twenty-seven samples of gastric juice varied from 1.12 to 7.07, with a mode about 1.6. Incubation of the juice at 37° C. for from one to six hours did not change the pH.

After determining the pH of pairs of samples of orange juice and gastric juice, these samples were mixed and the pH of the mixture was measured. A mixture of one part of orange juice to four of gastric juice was chosen because it was felt that a person would seldom take so much orange juice at a meal as to produce in the stomach a richer mixture than this. Table I shows that in the twenty-seven observations the pH of the mixture varied from 1.30 to 4.60, with a mode at 2.1. As one might have expected, the addition of orange juice lowered high gastric acidities and raised low gastric acidities.

In order to get some idea of the change in acidity

*I wish to thank Miss Catherine Sawyer for help which made this work possible.
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which might be produced in the stomach by digestion of the mixture of orange juice and food, the pH of each mixture of orange juice and gastric juice was measured after incubation at 37° C. for periods varying, in different observations, from one to six hours.

TABLE I

The pH of gastric juice, of orange juice and of a mixture of the two

Fresh			Incubated		
Gastric Juice	Orange Juice	Gastric Juice and Orange Juice	Gastric Juice	Orange Juice	Gastric Juice and Orange Juice
1.58	3.78	2.09	1.62	3.76	2.08
1.89		2.78	1.80		2.67
1.25		1.48	1.27		1.52
1.53	3.99	1.93	1.56	3.90	1.96
1.58		2.09	1.62		2.12
7.07		4.37			
6.42		4.42			
3.57		3.77	3.62		
2.08		2.99	2.16		2.99
1.41		1.72	1.46		1.76
1.40		1.76	1.44		1.78
6.26		4.60			
2.58	3.76	3.12	2.57	3.74	3.12
1.12		1.30	1.09		1.31
1.49		1.82	1.47		1.85
2.04		2.68	2.03		2.70
1.29		1.49	1.23		1.49
1.55		1.96	1.55		1.94
1.35	3.72	1.69			
1.30		1.68			
1.87		2.59			
1.66		2.01			
2.42		3.08			
1.63		1.86			
2.18		2.95			
1.26	3.63	1.58			
5.22	3.90	4.30	5.46	3.92	4.33

In no instance was any change in the pH observed.

In order to see what actually happens in a stomach when the juice of two and a half oranges is added to an ordinary American breakfast, two observations were made on healthy persons. For purposes of control, on the first day the volunteers ate a breakfast consisting of three tablespoonfuls of oatmeal, with cream and sugar, two slices of buttered toast, one soft-boiled egg, and one cup of coffee with cream. One and a quarter and two and a quarter hours after the meal, samples of gastric content were removed and the pH was determined. The following day a breakfast identical in quality and quantity to that eaten on the first day was consumed, together with 150 c.c. of orange juice. The data presented in Table II indicate

that in both of these observations the addition of orange juice did not have any effect on the pH of the gastric content.

DISCUSSION

The essential fact which emerges from that part of the study which was carried out in vitro is that, just

TABLE II

The lack of effect on pH when orange juice is added to a meal

Hours After Meal	Subject 1		Subject 2	
	Breakfast Alone	Breakfast with Orange Juice	Breakfast Alone	Breakfast with Orange Juice
1¼	1.65	1.60	2.04	2.27
2½	1.37	1.48	1.88	2.07

as one would expect, orange juice raised the pH or lowered the acidity of every gastric juice of which the pH was below that of orange juice, which, as will be remembered, was around 3.8. Since the pH of gastric juice from normal persons usually is below this level, one must conclude from the observations in vitro that normally the giving of orange juice should lower gastric acidity. Since patients who have peptic ulcer usually secrete gastric juice of which the pH is even lower than that of normal persons, one would expect the addition of orange juice to their diet to lower gastric acidity.

Unfortunately, the time available for this study did not permit more observations in vivo. In the two observations made, the addition of orange juice to the breakfast appeared to have no effect on the pH of the gastric content. This may have been due to the well-known fact that fluids tend to run out of the stomach rapidly, leaving solids behind. This is particularly true when the liquid is taken first on an empty stomach, as orange juice so often is taken in the morning. This point must be kept in mind in any study of the effect of a liquid on gastric acidity. The probability is that it will not stay in the stomach long enough to mix with the gastric secretion, and any effect it may have on the secretion will have to come from effects on the gastric glands, produced as the liquid is absorbed from the small bowel.

CONCLUSION

Judging from some observations made in vitro it seems probable that one need not worry about giving orange juice to patients who have peptic ulcer. If the orange juice should remain in the stomach long enough to have any effect on the acidity of the gastric content, this effect almost certainly would have to be a lowering one because orange juice is considerably less acid than is even normal gastric juice.

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Protamine Insulin and the High Carbohydrate-Low Fat Diet in Diabetes Mellitus*

By

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TWO very great advances have been made in diabetic therapy since Banting's epoch making discovery of insulin in 1922 that make it a joy to treat diabetes mellitus, when one is dealing with an intelligent, cooperative patient. Protamine insulin simplifies the treatment in that the average diabetic can give himself one dose of insulin each morning after he has examined his night and morning specimens of urine; and with the use of the high carbohydrate-low fat diet there is no longer any need for diabetics to endure the pangs of hunger.

Protamine insulin is simply insulin to which has been added zinc protamine in order to make the insulin less soluble so that it will be more slowly absorbed, and therefore its effect more prolonged. Hagedorn and his associates in Copenhagen demonstrated that the rate of absorption of insulin could be retained and its effect prolonged for at least 24 hours by suspending it in a protamine mixture, thus imitating the normal continuous secretion of insulin by the islands of Langerhans of the pancreas. Leyton in 1929 made an unsuccessful effort to prolong the use of insulin by suspending it in oil, and the Hagedorn group made experiments with a number of substances before they found that a combination of the monoproamines and insulin, forming what they called protamine insulate, would retard the absorption of insulin. At first the buffer solution of protamine was mixed by the patient with regular insulin; but more recent investigations, particularly by Best, Kerr, Campbell and Fletcher in Toronto, it was found that a solution of zinc protamine combined with regular insulin formed a stable compound that can be dispensed in ampules so that one c.c. of zinc protamine insulate contains 40 standardized units of insulin. The zinc protamine insulate is now called protamine insulin.

The work of Hagedorn and his associates has been verified by a number of diabetic clinicians in the United States and Canada, including Joslin, Root, White, Marble and Stotz; Frederiek M. Allen; Smith and Grishaw; Sprague, Blaum, Osterburg, Kepler and Wilder; John; Best, Kerr, Campbell and Fletcher; and Anthony Sindoni, Jr. The clinicians mentioned, and others who have reported studies with protamine insulin, agree that its use in uncomplicated diabetes has many advantages over the regular insulin; and in less than two years it is safe to say that protamine insulin has replaced regular insulin in the vast majority of cases now under treatment by physicians experienced in the management of diabetes mellitus;

though in many cases one or more doses of regular insulin is used in addition to the protamine insulin.

Our experience with about 100 diabetics in private practice, in which we have used protamine insulin during the last 18 months has convinced us of the many advantages of protamine insulin over regular insulin; though in the beginning we were skeptical regarding the enthusiastic claims in some of the early published reports of clinicians. Perhaps a reason for our early skepticism was a severe insulin reaction in a child, whose diabetes was under perfect control by the use of the regular insulin adjusted to a diet adapted to the patient's nutritional needs. Since that time we have not had a severe reaction, though in several cases blood sugar readings in diabetics using protamine insulin have been low. One patient had a morning fasting blood sugar of 25 milligrams per cent, though she felt fairly well. A reduction in the dose of protamine insulin maintained her blood within normal limits, though she at times showed small amounts of sugar in her urine.

The Hagedorn group used the protamine insulin in one dose at night, with an added dose of regular insulin before the morning meal. American clinicians, however, soon learned that with the average case a single morning dose on arising will maintain the patients blood sugar within or near the normal range and prevent glycosuria for from 12 to 24 hours. It is a mistake to claim protamine insulin can maintain a level blood sugar curve throughout the 24 hours; because Harrop, in studying half hour blood sugar readings in a series of cases, showed that they were quite marked fluctuations, more below the normal levels. The writer had the privilege of seeing a number of Harrop's cases in the metabolic wards of Johns Hopkins Hospital in which there were quite low blood sugar levels, yet the patients seemed quite comfortable.

HYPOGLYCEMIC REACTIONS FROM PROTAMINE INSULIN

It seems that the diabetic using protamine insulin can stand hypoglycemia better than when the low blood sugars are induced by overdoses of regular insulin. This phenomenon may be explained by the fact that in induced hyperinsulinism from overdoses of regular insulin the blood sugar fall is more rapid, and therefore the reactions occur more frequently than in the more slowly acting protamine insulin when the patient has time to become adjusted to relatively low blood sugars. This also accounts for the more prolonged reactions when they occur following the use of protamine insulin. Sometimes it is necessary to use large doses of orange juice, honey or corn syrup, or

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dextrose intravenously, repeated every few minutes until the hypoglycemic reactions from protamine insulin subside.

Nausea and vomiting are not frequent in hypoglycemic reactions from regular insulin; but in several of our cases of reactions from protamine insulin

keep a record of the examinations of urine, the amounts of carbohydrates, proteins, and fats used each day, and the amounts of protamine insulin used each day. Many of them have kept their urine sugar free with only one dose of protamine insulin a day. They have been instructed not to increase the pro-

TRIAL DIET NO. I

165 to 175 grams carbohydrate, 60 grams protein, 10 grams fat. Five meals a day, at 7 and 10 a. m.; and 1, 4 and 7 p. m.

AMOUNT			FOOD	APPROXIMATE FOOD VALUES			
Gms.	Oz.	Household Measures		Ch.	P.	Fat	Cals.
16	½	1 Slice	Whole wheat bread	8	2	0	40
19	½	1 Tblspn.	Honey	15	0	0	60
240	8	1 Glass	Churned buttermilk (fat free) or skimmed milk	10	10	2	98
			Food value of each meal	33	12	2	198
			Total food value of 5 meals approximates	165	60	10	990

Note: A banana of average size (6½ inches long by 1½ inches in diameter) or an apple (3 inches in diameter) or an orange (2½ inches in diameter) may be substituted for the bread, honey, and milk at any or all the five feedings.

nausea and vomiting have been pronounced. The nausea and vomiting have been promptly relieved by the intravenous use of a 50 c.c. ampule of a 50 per cent dextrose solution given slowly, intravenously. In fact we believe that in any case of a hypoglycemic reaction from the use of protamine insulin, that the dextrose should be given intravenously, because in such cases the patient may vomit the soluble carbohydrates when given orally and the reaction continue unless the dextrose is given intravenously.

Early reports on the use of protamine insulin urged the necessity of hospitalizing diabetics when making the change from regular insulin to protamine insulin, or in beginning its use with new patients; but at least three-fourths of our approximately 100 cases in which protamine insulin has been used have been ambulatory patients, and in only one of them has there been a severe reaction.

CHANGING FROM REGULAR TO PROTAMINE INSULIN

Our rule in changing a patient from regular insulin to protamine insulin is to begin with a morning dose of approximately half the total daily amount of regular insulin that the diabetic has been using to keep his urine sugar free, and in addition give about three-fourths the morning dose of regular insulin. The patient is instructed to examine his night and morning specimens of urine, and if sugar is present, to increase the protamine insulin by from 3 to 6 units each day until his urine becomes sugar free; then to reduce the dose of protamine insulin by 5 units, because of the possible cumulative effect of the protamine insulin. The morning dose of regular insulin is omitted when the morning blood sugar is within normal limits, or when the morning specimen of urine is sugar free.

In many cases of intelligent cooperative diabetics who have been controlling their diabetes with regular insulin adjusted to the high carbohydrate-low fat diets they have been accustomed to use in keeping their urine sugar free, the transition is made while they continue their regular work. They are instructed to

take protamine insulin when there was only a small amount of sugar in the urine, that it is better to have a small amount of sugar in one specimen of urine in a day, than to run the risk of a protamine insulin reaction from an increased dose.

The new patient who has not used regular insulin and who has not learned to weigh and measure his food, examine his urine, and give himself insulin when necessary, should be hospitalized for a few days under the observation of a diabetic clinician if possible, until his diet and protamine insulin have been adjusted and the patient can be taught how to care for himself in diabetes. In a small number of our cases it has been necessary to use in addition to the single dose of protamine insulin a small dose of regular insulin at the same time or before the noon or evening meal.

Protamine insulin can never take the place of regular insulin when quick action is desired as in acidosis, with or without coma. After the diacetic acid and acetone have disappeared from the urine and the blood sugar has been reduced practically to normal, the protamine insulin may be begun, to which is added smaller doses of regular insulin for one or two days, when it may be left off, if the patient's urine continues free from acetone and diacetic acid.

The regular insulin is preferable to protamine insulin in preparing diabetics for operation and in caring for them until the surgical hazard is over. If, however, the surgical diabetic is using protamine insulin and is controlling his diabetes, his dose may be reduced by about 20 or 30 per cent, and guarded with dextrose intravenously, if necessary. The regular insulin in appropriate doses may be added in the surgical case, using protamine insulin.

HIGH CARBOHYDRATE-LOW FAT DIETS IN DIABETES MELLITUS

We use a high carbohydrate-low fat diet in at least nine-tenths of our adult diabetics and believe that it has many advantages over the high fat low carbohydrate diet, as formerly used. We have had many adult patients using approximately 300 grams of carbohy-

drate, 75 grams of protein and 50 or 60 grams of fats with sufficient insulin dosage to control their diabetes, and switch them without changing their diet, to the use of protamine insulin, without the slightest trouble. It is important, however, to give three smaller meals with a glass of buttermilk or skimmed milk, an orange,

high carbohydrate-low fat diet overcome the objections offered by Sindoni to using the new insulin with high carbohydrate-low fat diets.

It seems rational in the treatment of diabetes mellitus (hypoinsulinism) to adopt a dietary regimen directed towards increasing insulin production, and in

TRIAL DIET NO. II

Approximating 200 grams carbohydrate, 60 grams protein, 40 grams fat

AMOUNT			FOOD	APPROXIMATE FOOD VALUES			
Gms.	Oz.	Household Measures		Ch.	P.	Fat	Cals.
			BREAKFAST				
100	3½		Orange, or apples, or 150 gms. ½ grapefruit, or ½ cantaloupe..	12	1	0	52
100	3½	6 cooked	Oatmeal, or 30 gms. (medium serving) of any dry cereal as rice flakes, corn flakes or wheat flakes—no bran	12	3	1	69
50	3	½ glass	Skimmed milk	5	3	0	29
16	½	1 slice	Whole wheat bread or white bread, corn muffin, or small piece corn bread	8	2	0	40
10	½	1	Honey	15	0	0	60
10		1 pat	Butter	0	0	9	81
				52	9	10	331
<i>Three Hours After Breakfast:</i>							
100	(6½"x1½")		Medium sized banana, or 200 gms., medium size apple, or orange	30	1	0	130
DINNER							
45	(3"x1½")		Lean meat—steak, roast, lamb, ham, liver, chicken, or fish.	0	11	0	125
150	3½	5	Any one or two 5 per cent vegetables as turnip greens, spinach, cabbage, cauliflower, string beans, asparagus	4	2	1	33
75	3½	5	Any 10 per cent vegetable as carrots, squash, English peas, beets, or turnips	7	1	0	32
150	5		Irish potatoes or 75 gms. sweet potatoes	30	3	1	136
16	½	1 slice	Whole wheat bread, or white bread, or corn muffin or piece c. bread	8	2	0	40
				49	29	11	336
<i>Three Hours After Noon:</i>							
Medium sized banana, orange or apple.							
SUPPER OR LUNCHEON							
45	½	3	Meat substitutes: Cottage cheese, or the same amount of American, Swiss or other cheese (providing butter is left off); or 50 gms. (3 tablespoonsful) of butter beans, lima beans, or 100 gms. (6 tablespoonsful) English peas	2	9		49
150	3½		Cole slaw, carrots, celery, radishes, tomatoes or any raw vegetable (only 11	3	1	0	16
16	½	1 slice	Whole wheat bread or white bread, or 1 small piece corn bread	8	2	0	40
100	3½		Baked apples, or medium serving of any fruit (without cream), berries, watermelon, honey dew melon or cantaloupe	12	1	0	52
		1	Mayonnaise of mineral oil	0	0	0	0
10		1 pat	Butter	0	0	9	81
				25	13	9	238
Approximate food value for day				200	50	40	1360

Medium sized banana, or orange, or glass of buttermilk at bedtime and every 2 or 3 hours if awake at night.

or a banana, or an apple, or bread and honey three hours after breakfast, after the noon meal and at bedtime. High carbohydrate-low fat meals are more rapidly digested, absorbed and metabolized, than those of high fat content when the stomach empties more slowly, hence the necessity of food between meals, at bedtime and every 2 or 3 hours if the patient is awake at night in using protamine insulin with the patient using the high carbohydrate-low fat diets. The frequent feedings in using protamine insulin and the

promoting the storage of glycogen in the liver, thus facilitating carbohydrate metabolism. On such a dietary regime, blood sugar levels are lowered, the severity of the disease is ameliorated, the dangers from complications, such as acidosis, arteriosclerosis and gangrene are decreased.

The metabolism of carbohydrates depends largely upon the amount of insulin in the blood, or the degree of its utilization. The ingestion of sugars and starches stimulate insulin production. The studies of Lennox

seem to show that the larger the quantity of ingested glucose the greater the degree of stimulation of the blood sugar regulating mechanism of the body. He found that the ingestion of 1.5 grams of glucose per

could be no increase in function. Soskin and Campbell, however, have shown that depancreatized dogs, when placed on a pure carbohydrate diet, will improve temporarily and live longer than if placed on a diet

TRIAL DIET No. III

Approximating 250 grams carbohydrate, 65 grams protein, 40 grams fat

AMOUNT			FOOD	APPROXIMATE FOOD VALUES			
Gms.	Oz.	Household Measures		Ch.	P	Fat	Cals.
150	5		BREAKFAST				
			Orange, or apples, or 150 gms— $\frac{1}{2}$ grapefruit or $\frac{1}{2}$ cantaloupe	16	1	0	52
100	$3\frac{1}{2}$	6 cooked	Oatmeal, or 30 gms. (medium serving) of any dry cereal as rice flakes, corn flakes, or wheat flakes—no bran	12	3	1	69
90	3	$\frac{1}{2}$ glass	Skimmed milk	5	3	0	29
32	1	1 slice	Whole wheat or white bread, 2 corn muffins or 2 small pieces c. bread	16	4	0	80
40	$1\frac{1}{4}$	$2\frac{2}{3}$	Honey	32	0	0	128
10			Butter	0	0	9	81
				81	11	10	439
			<i>Three Hours After Breakfast</i>				
100	($5\frac{1}{2}$ "x $1\frac{1}{2}$ ")		Medium size banana, or 200 grams medium size apple, or orange	30	1	0	130
			DINNER				
45	(3"x2"x $\frac{1}{2}$ ")		Lean meat—steak, roast, lamb, ham, liver, chicken or fish	0	11	9	125
150	$3\frac{1}{2}$	5	Any one or two 5 per cent vegetables as turnip greens, spinach, cabbage, cauliflower, string beans or asparagus	4	2	1	83
75	$2\frac{1}{2}$	5	Any ten per cent vegetable as carrots, squash, English peas, beets or turnips	7	1	0	32
150	5		Irish potatoes, or 74 gms. sweet potatoes	30	3	1	136
30	1	1 slice	Whole wheat bread or white bread, or 2 corn muffins, or 2 small pieces corn bread	16	4	0	80
240	8		Buttermilk or skimmed milk	10	10	2	98
				67	31	13	604
			<i>Three Hours After the Noon Meal:</i>				
			Medium sized banana or glass of buttermilk or skimmed milk.				
			SUPPER OR LUNCHEON				
45	$1\frac{1}{2}$	3	Meat substitute: Cottage cheese, or the equivalent of American cheese—provided butter is left off; or 50 gms (3 tablespoons) butter beans, lima beans or 10 gms. (6 tablespoons) English peas	2	9	0	49
150	$3\frac{1}{4}$		Cole slaw, carrots, celery, radishes, tomatoes or any 1 raw vegetable	3	1	0	16
30—	1	2 slices	Whole wheat or white bread, or 2 corn muffins, or 2 small pieces of corn bread	22	5	0	110
100	$3\frac{1}{4}$		Baked apple, or medium serving of any fruit (without cream) berries, watermelon, honey dew melon, or cantaloupe	12	1	0	52
240	8	large gl.	Buttermilk or skimmed milk	10	10	2	98
			Butter	0	0	9	81
				49	26	11	406
			Approximate food value for the day	250	65	40	1620

kilo of body weight caused, after the temporary rise, a greater degree of hypoglycemia than 0.75 grams per kilo.

Sweeney, of Dallas, Texas, has demonstrated that diets with high carbohydrate content are followed by lower blood sugar levels, thus increasing sugar tolerance, whereas diets with high fat content cause hyperglycemia and diminished sugar tolerance. If carbohydrates stimulate insulogenesis, it would seem that a high carbohydrate diet would increase the output from a poorly functioning pancreas of the diabetic, unless all the islet cells have been destroyed by a previous disease of the pancreas, when it is obvious that there

containing fats. In other words, a high carbohydrate diet will postpone the acidosis (ketosis) and coma from which depancreatized animals die.

Best, who collaborated with Banting in the discovery of insulin and who succeeded Macleod as Professor of Physiology in the University of Toronto, seems in accord with the theory that the ingestion of carbohydrates stimulate the insulinogenic apparatus. In a recent address Best said: "The evidence seems overwhelming that a rise in sugar content of the blood increases the output of insulin."

Recent results obtained from a high carbohydrate-low calorie diet in diabetes, reported by Sansum

Geyelin and Rabinowitch, seems to show that the insulogenic function of the pancreas may be at least partially restored by resorting to the use of quantities of carbohydrate not dreamed of by clinicians prior to the insulin era in the treatment of diabetes. Certainly such diets increase insulin efficiency so that, according to the experience of a number of clinicians, one unit of insulin will in many cases metabolize two or three times as much carbohydrate on the new diabetic diets as when the same patient was on the low carbohydrate-high fat diet.

Sansum, who in 1926, reported his favorable results from the use of a high carbohydrate and relatively low fat diet, believes that on such a diet there may be actual regeneration of the damaged islands of Langerhans, and he cites Shields Warren and Root as having demonstrated that the islands of Langerhans in diabetics can and do regenerate. The fact that on a higher carbohydrate diet diabetics improve in every way, requiring a lower insulin dosage, Sansum believes is evidence of greater efficiency of the patient's insulogenic apparatus, since on the high carbohydrate-low fat diets many diabetics improve to the extent that they cease to need insulin and can metabolize a normal diet. Sansum suggests that it may be another step towards the curative treatment of diabetes.

Woodyatt doubts the theory that the high carbohydrate-low fat diets actually cause a regeneration of the islands of Langerhans. He is of the opinion that while it is true that on the high carbohydrate-low fat diet no more insulin may be required to keep the diabetic's urine sugar free and his blood sugar normal than when he was taking one-half of the carbohydrates and a high fat diet, he cannot metabolize more calories than when most of his food was made up of fats. Woodyatt suggests that on the high carbohydrate-low fat diets much of the ingested carbohydrate is changed into fat and then oxidized. This observation is important in that it explains the necessity for reducing the fats in using the high carbohydrate diet.

Aldersburg and Porges, in Vienna, no doubt working independently of Sansum, Geyelin and Rabinowitch, have had equally good results with the high carbohydrate-low fat diets. They believe that the value of this diet comes from the fact that there is increased storage of glycogen and decreased deposits of fats in the liver. They claim that carbohydrate metabolism, both of normal individuals and diabetics, is increased when the glycogen deposits of the liver are filled; and that when there is an excess of fat storage in the liver the ability to metabolize sugar is diminished.

While carbohydrates stimulate insulogenesis there is ample evidence to prove that fats depress the function of the islands of Langerhans. Rabinowitch cites Allen as having demonstrated that dogs partially depancreatized, to the border line of diabetes, can be made diabetic on a fat-protein diet. Shepherdson states that blood sugar levels will rise on a low carbohydrate diet. He quotes Weeks, Renner and Wishart as having observed in a study of epileptic patients on high fat diets that in every case they developed hyperglycemia.

If a diet high in carbohydrates tends to lower blood sugar levels, whether by stimulating insulogenesis, or by promoting the deposit of glycogen in the liver, it would seem that we have been wrong in giving our diabetics low carbohydrate-high fat diets, and such

seems to be a fact. Therefore, we should correct our mistakes and reverse the ratio of carbohydrates and fats. Practical experience in the management of diabetes on high carbohydrate-low fat diets over a period of ten years by Geyelin and the excellent results reported by Rabinowitch with his "high carbohydrate-low calorie" diet in more than 1000 cases of diabetes seem to indicate that in diabetes mellitus the ratio of carbohydrates to fats should be between 3 and 4 to 1.

HIGH CARBOHYDRATE-LOW FAT DIETS PREVENT ACIDOSIS AND RETARD ARTERIOSCLEROSIS

In dieting a diabetic there are other equally important considerations besides the effort to stimulate increased insulin production. The question of an adequate, well balanced diet, with the proper mineral and vitamin content is important, likewise the prevention of acidosis and arteriosclerosis should be considered in dieting the diabetic. Certainly a high carbohydrate-low fat diet tends to prevent acidosis. Sansum says that even on a carefully balanced diet over exercise will produce acidosis from imperfect metabolism of the individual's own fat. Therefore, on the high fat diet that we formerly used there was always the tendency to acidosis (ketosis). Unquestionably the high carbohydrate-low fat diet lessens the hazard of acidosis and coma in diabetes.

Arteriosclerosis in the diabetic, resulting in gangrene, coronary disease, nephritis, apoplexy and other complications, is receiving a great deal of attention at this time. Ignatowsky, and other German investigators produced arteriosclerosis in animals by feeding them on high fat diets. They believe that hypercholesterinemia was the cause of the degenerative arterial changes in experimental arteriosclerosis. Joslin and Root and other American investigators, have contributed much to the available knowledge of the incidence of arteriosclerosis in diabetes. Rabinowitch cites Shields Warren as having made the statement that he "had never performed an autopsy on a diabetic of any age who had had diabetes for five years without finding evidences of arteriosclerosis."

Hypercholesterinemia from high fat diets is accepted as an important cause of the degenerative arterial changes in diabetes. Rabinowitch has found that the high cholesterol content of the blood in diabetics is usually reduced to normal by his "high carbohydrate-low calorie" diet. At the meeting of the American College of Physicians in Philadelphia in 1935 he presented a report on the cholesterol content of the blood in diabetics on high carbohydrate-low calorie diets over a period of five years. There was the return to normal cholesterol content of the blood in nearly all the diabetics so treated.

Rabinowitch and his associates in the Montreal General Hospital made careful studies of their diabetics at the beginning of treatment, not only as to the cholesterol content of the blood, but as to clinical evidences of arteriosclerosis. They found from many thousand blood cholesterol determinations that with a few exceptions at the beginning of treatment of their diabetics they had hypercholesterinemia. The cholesterol content of the blood of the diabetics on Rabinowitch's high carbohydrate-high fat diet and insulin, was maintained within the normal limits, whereas the control cases kept on a low carbohydrate-high fat diet continued high.

Clinical studies on the diabetics who had been treated with Rabinowitch's high carbohydrate-low calorie diet and insulin over a period of five years, showed that in younger diabetics they did not have evidences of arteriosclerosis; whereas the control group treated with low carbohydrate-high fat diets

also showed a much lower incidence of acidosis and coma among diabetics on a high carbohydrate-low calorie diet than among those treated with the low carbohydrate-high fat diets. Rabinowitch's studies combined with those of Geyelin, Sansum, Aldersburg and Porges, and others seem to prove conclusively that

TRIAL DIET NO. IV

AMOUNT			FOOD	APPROXIMATE FOOD VALUES			
Gms	Oz	Household Measures		Ch	P.	Fat	Cals
			BREAKFAST				
100	3½		Orange, or apple, or 150 gms—½ grapefruit, or ½ cantaloupe	12	1	0	52
150	3¼	8 cooked	Oatmeal or 45 grams (large serving) of any dry cereal as rice flakes, corn flakes or wheat flakes—no bran	18	6	2	103
45	1½	3 slices	Whole wheat or white bread, or 2 corn muffins or 2 small pieces corn bread	22	5	0	110
90	3	½ glass	Skimmed milk	5	3	0	29
45	1½	3	Honey	45	0	0	260
10	1½	1 pat	Butter	0	0	9	81
			Total Food Value	102	15	11	635
			Three Hours After Breakfast				
150	(6½' x 2"x1")		Medium size banana or 250 gms medium size apple or orange	30	1	0	130
			DINNER				
60			Lean meat—steak, roast, lamb, ham, liver, chicken or fish	0	14	12	164
150	3½	5	Any one or two 5 per cent vegetables as turnip greens, spinach, cabbage cauliflower, string beans or asparagus	4	2	1	33
75	2¼	5	Any ten per cent vegetable as carrots, squash, English peas, beets or turnips	7	1	0	32
150	5		Irish potatoes or 75 gms sweet potatoes	30	3	1	136
30	1	2 slices	Whole wheat or white bread, or corn muffins or 2 small pieces corn bread	16	4	0	80
100	3½		Baked apple	12	1	0	52
			Total Food Value	69	25	14	497
			Three Hours After Noon Meal				
			Medium size banana or orange, or glass of butter milk or skimmed milk				
			SUPPER OR LUNCHEON				
60	1½	4	Meat substitute Cottage cheese or same amount of American Swiss or other cheese provided butter is left off, or 50 gms (3 tablespoons) butter beans, lima beans or 100 gms (6 tablespoons) English peas	2	13	1	69
150	3¼		Cole slaw, radishes, carrots, celery, tomatoes or any raw vegetable	3	1	0	16
		1	Mineral oil mayonnaise	0	0	0	0
45	1½	3	Whole wheat or white bread or 2 small pieces corn bread or 2 corn muffins	22	5	0	110
210	8	1 glass	Buttermilk or skimmed milk	10	6	8	135
15	1½	3	Honey	45	0	0	260
100	3¼		Baked apple or medium serving of any fruit (without cream), berries watermelon honey dew melon or cantaloupe	12	1	0	52
			Butter	0	0	9	81
			Total Grams	94	26	18	724
			Total food value for the day	300	75	50	1950

Glass of buttermilk or skimmed milk, or medium sized banana or orange at bedtime and every 2 or 3 hours if awake at night

showed high percentage of degenerative arterial changes. In the older diabetics on the high carbohydrate-low calorie diet there was a decreased incidence of cardiac and arterial diseases, including angina pectoris, coronary thrombosis and apoplexy.

Rabinowitch's experience over the five year period

diabetics are happier and more efficient on a high carbohydrate-low fat diet, and that the incidence of the complications of diabetes have been reduced very materially by the change from low carbohydrate-high fat diets to an inverse ratio of carbohydrates to fats.

We are convinced of the soundness of the nutritional

principles upon which the high carbohydrate-low fat diets are based; and our experience with this innovation in diabetic therapy over a three year period has been so pleasing that we have adopted it whenever practicable in uncomplicated diabetes. This does not mean that we use the same diet in every uncomplicated case of diabetes; because no two diabetics present exactly the same problems in nutrition and treatment, and it is just as necessary to prepare a diet suited to the needs of the individual under treatment as when the low carbohydrate-high fat diets were used.

SIMPLIFIED DIETS

We have, however, prepared a series of trial diets which may be used with the average uncomplicated case of diabetes, modifying them to meet the needs of the individual under treatment of diabetes. In order to facilitate their use by the general practitioner, estimates of the quantities of each article of food in household measures have been added.

It is highly desirable for the diabetic to have a few days of preliminary diet before placing him upon his maintenance high carbohydrate-low fat diet. Rabinowitch employs what he calls the "ladder diet" to determine whether or not the patient can be rendered sugar free without insulin. On the first day he gives the patient nothing but water, clear well salted fat free broth, tea and coffee. It seems to me that a day of starvation is unnecessary and that the tolerance of the diabetic can be raised more quickly by giving the soluble carbohydrates for one or two days.

For a number of years when a diabetic with diacetic acid in his urine came in for treatment we have given him, every 2 or 3 hours, on the first day 250 c.c. (8 ounces) of dextrose orangeade. This really delicious drink is prepared as follows: 3 ounces of orange juice and 5 ounces of a 5 per cent dextrose solution. It is given cold or hot. The carbohydrate value is 17 grams so that if it is given every 3 hours from 7:00 a. m. to 7:00 p. m. and every 5 hours if awake at night, it is the equivalent of 90 to 144 grams of carbohydrate the first 24 hours of treatment. In addition 8 ounces (250 c.c.) of water is given one-half hour before the first feeding and every 3 hours (1½ hours after the dextrose orangeade) day and night so that the diabetic with the diacetic acid and sugar will find them disappearing from the urine in 24 hours in many cases of moderately severe diabetes; and in the more severe cases with a tendency to acidosis, diabetics usually will become sugar and diacetic acid free by giving 10 units of insulin before the 7:00 a. m., 1:00 and 7:00 p. m. feedings. If there is the tendency to coma, 5 or 10 units of insulin may be given before the other feedings.

In beginning the treatment of diabetes with the ambulatory patient, on the first day we give what we call Trial Diet No. 1. It consists of five meals, one every 3 hours from 7:00 a. m. to 7:00 p. m., each made up of the following: 1 slice of whole wheat bread ½ inch thick, 1 tablespoonful of strained honey, 8 ounces of churned (fat free) butter milk. The total food value of this diet approximates 165 grams carbohydrates, 60 grams protein and 10 grams of fat. Water is given freely between feedings. In the South where churned buttermilk is in common use, and generally liked, this diet will surprise and delight the diabetic who has

been starved for bread, milk and sweets. If the patient objects to the buttermilk he may have skimmed milk, or if he objects to that, he may be given an orange, apple or banana for each feeding.

If the diabetic's urine becomes sugar free in one or two days, as it usually does in mild cases, no insulin is given, and Trial Diet Number 2 is given. This consists of approximately 200 grams of carbohydrate, 50 grams of protein and 40 grams of fat. If on this diet the diabetic's urine is sugar free, Trial Diet Number 3, consisting of 250 grams of carbohydrate, 65 grams of protein and 40 grams of fat, is given for one or two days. If the urine remains sugar free, Trial Diet No. 4, 300 grams carbohydrate, 80 grams protein and 50 grams of fat, is given. This diet, with food value of about 1950 calories will give the average adult diabetic sufficient food to satisfy his appetite and maintain his normal weight and efficiency.

DIETING UNDERWEIGHT AND OVERWEIGHT DIABETICS

If the underweight mild diabetic does not gain weight on Trial Diet Number 4 his carbohydrates may be increased, giving more bread, potatoes and honey until he is getting approximately 400 grams of carbohydrates a day; and the fats may be increased to 90 grams a day by giving an extra pat of butter at each meal making a total daily food intake of about 2700 calories a day. If the underweight diabetic is a laborer, or if he takes a great deal of exercise, his carbohydrates may be increased to 500 grams and fats to 120 grams, thus giving him about 3400 calories a day. When the underweight diabetic has gained to within 10 per cent of the standard weight, his diet is decreased by cutting down his bread, potatoes and other carbohydrates and reducing his fats by eliminating the pat of butter at each meal, until the physician has worked out the diabetic's maintenance diet, i.e., the amount of food upon which the individual can carry on his work with comfort and maintain a weight of 5 or 10 pounds under the insurance companies' estimates of the optimal weight for his age and height.

If the diabetic is overweight his carbohydrates are decreased by leaving off a slice of bread at each meal and reducing the amount of potatoes, rice and other starchy foods until his carbohydrate intake is about 200 grams per day, and his fats are reduced by taking off one less pat of butter at a meal to about 50 grams a day. He is kept on this low calorie diet until he has decreased in weight until he weighs about 5 or 10 pounds below the standard weight for his height and age. Then his diet is increased to Trial Diet Number 4. This maintenance diet is decreased if there is again the tendency to gain weight.

Rabinowitch insists that on his "high carbohydrate-low calorie diet" the patient should become, and remain 5 to 10 pounds under the normal weight. This he calls "mild undernutrition" a highly desirable state in promoting the health, efficiency and longevity for the diabetic.

Uneducated diabetics should be given diets consisting of foods that they can get at home estimated in household measures, and if they have stamina and character they may get as good results in the management of their malady as if they had gram scales and could calculate their own menus. Poverty and ignorance are not insurmountable handicaps for diabetics;

but with the irresponsible, self indulged diabetic, whether educated or not, the paths of overindulgence "lead but to the grave."

If, after two or three days on Trial Diet Number 1, there is still sugar in the diabetic's urine, he is given from 6 to 12 units of Protamine Insulin at seven a. m., and if in twenty-four hours his urine still contains sugar, the Protamine Insulin is increased to 15 to 21 units. If, in another twenty-four hours the sugar has not disappeared from his urine, 30 to 40 units of Protamine Insulin are given on arising. When one of the three daily specimens has become sugar free the diet is increased to Trial Diet Number 2, and if the sugar returns in the urine, the Protamine Insulin dosage is increased until the urine is sugar free. Then Trial Diet Number 3 is given, and if the sugar reappears in the urine, the Protamine Insulin is increased by three to six units each day until his urine becomes sugar free.

The diet is increased to Trial Diet Number 4 in the same way, increasing the insulin slowly until the urine is sugar free. After the patient's maintenance diet and his Protamine Insulin dosage have been worked out as above described, he is kept on the same diet with the same dose of insulin for several weeks, the effort being to keep the urine sugar free without the patient having insulin reactions. If insulin reactions occur, the Protamine Insulin is reduced or the food increased.

We have switched a number of patients from diets of 150 grams of carbohydrates, 60 grams of protein and 120 to 180 of fat to 300 grams carbohydrates, 60 grams proteins, and 50 grams fat, continuing the same dose of insulin they had been using for months or years; and in a few days they would begin to have hypoglycemic reactions, so that the dose of insulin had to be reduced to 25 to 50 per cent. In some of the mild cases requiring from 15 to 30 units of insulin a day, the insulin has been discontinued entirely. In other words on a diet approximately 250 or 300 grams of carbohydrate a day, less insulin was required than when they were getting less than half the amount of carbohydrates and a high fat diet.

Insulin should never be discontinued except on the advice of a physician who has studied the case and one who is qualified to treat the disease. In such cases the insulin dosage is gradually reduced and, if the sugar does not reappear in the urine, the insulin is discontinued. The patient should be made to realize that he should never over-eat, either of carbohydrates or fats; that a food debauch may break his carbohydrate tolerance and he will then have to use insulin again.

Insulin is not habit forming, but it should not be left off suddenly without at the same time reducing

the diet in proportion to the amount of insulin used. The patient taking insulin should keep on hand an adequate supply, but if he cannot get insulin, he should reduce his food by one-half, or even two-thirds and leave off the fats altogether, because the principal danger from leaving off the insulin suddenly is acidosis, or even coma. It is not altogether the leaving off of the insulin that is harmful, but the greatest danger lies in continuing the extra food that the diabetic cannot metabolize without using insulin.

The millennium for the diabetic has not yet been attained; but with the use of vitamin rich, high carbohydrate-low fat diets adapted to the needs of the individual, and with only a morning dose of Protamine Insulin adjusted to the patient's diet, there is no reason for uncomplicated diabetes to interfere with efficiency or shorten life. It formerly was said "once a diabetic always a diabetic," and undeniably any person who had had diabetes should be careful about his diet for the rest of his life; but what Aldersberg and Porges call "curvative treatment of diabetes mellitus" with the high carbohydrate-low fat diet, enables many persons with uncomplicated diabetes mellitus to live the abundant life without insulin.

Recent experience with Protamine Insulin and the high carbohydrate-low fat diet suggest that the insulogenic apparatus of the diabetic may be restored to practically normal function in some of the mild and moderately severe cases of diabetes. We have had a number of patients who, on a high fat low carbohydrate diet had been taking regular insulin for varying periods—one of them 10 years, but who after a few weeks or months on a high carbohydrate-low fat diet and gradually reduced doses of Protamine Insulin, have been able to maintain normal blood sugar levels and remain aglycosuric without insulin. In the last month we have had four patients who have given up the Protamine Insulin and were living on maintenance diets ranging from 250 to 300 grams of carbohydrate, 60 to 75 grams of protein and 50 to 60 grams of fats.

There is reason to believe that an excess of fats in the diet inhibits insulogenesis and that such diets continued for a long time may lower tolerance permanently; whereas carbohydrates stimulate the secretion of insulin and when diabetics are given a high—but not too high—carbohydrate-low fat diet continued for some time, there are grounds for believing that there may be a permanent increase in sugar tolerance. Certainly practical experience with high carbohydrate-low fat diets and the use of Protamine Insulin has shown that in the mild and moderately severe cases of diabetes there is reasonable hope for an approximate cure.

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Hydrophilic Colloidal Diet*

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HYDROPHILIC COLLOIDAL DIET

HYDROPHILIC colloids form the substratum of all living protoplasm. They possess the property of readily taking up and giving off the substances essential to cell life. Precipitation of the hydrophilic colloids of protoplasm causes cell death.

PHYSIOCHEMICAL CONSIDERATIONS

Man's food in the raw state consists largely of hydrophilic colloids. The heat of cooking on the other hand—to mention only the physiochemical change—precipitates the colloids of our diet. This change in colloidal state alters the hydration capacity of our foods so as to interfere with their ability to absorb digestive juices. The amount of interference depends upon both the degree of thermo-concentration and the specific character of the colloidal medium itself. Certain colloids will withstand more heat than others; for instance, cellulose of vegetable origin and certain pectins will stand a greater temperature without being precipitated than the proteins of animal origin.

Any hydrophilic colloid, be it living protoplasm or a mineral jelly, has a certain hydration capacity under given conditions. By varying the physiochemical conditions surrounding such a colloid, it may be made to expand or contract. In the laboratory the expansion and contraction of colloids can be controlled within set limits at will.

Familiar laboratory experiments dealing with the absorption of chemicals and fluid by hydrophilic colloids are the experiments described by M. H. Fischer

(1). If two gelatin squares of similar weight are immersed in finger bowls, one containing distilled water, the other a solution of hydrochloric acid of 1/100 normal concentration, we find two interesting phenomena. First, the gelatin square in the acid expands at a much greater rate than the square in the water. Second, the solution about the square in the acid medium becomes almost of the same hydrogen ion concentration as distilled water. Now, if the acid solution is made stronger, the gelatin is digested, making a colloidal suspension, and unless too great a concentration of acid is present the acidity of the solution approaches neutrality. On the other hand, gelatin precipitated by heat fails to take up water or acid.

PHYSIOLOGIC APPLICATION

If man did not cook his food, there would be no need for the addition of any hydrophilic colloid to his dietary. Uncooked foods contain sufficient hydrophilic colloid to keep his gastric mucosa in excellent condition. On the other hand, man living largely on cooked foods presents a different problem. Recall the description of the stomach contents so vividly described in medical school days, as consisting of several layers, each layer assuming its position by virtue of its specific gravity; meat first, then vegetables and fruits followed and interspersed by the mashed potatoes, and last the water layer with its scum of fat; and how this was churned around and had poured into it sufficient gastric juices to digest the meal in one and one-half to four hours if all was well. If such gastric contents are removed and examined, the aqueous layer is found to be strongly acid, the degree

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differing with the individual. The digestive action takes place between the food particles and the gastric mucosa, which to be sure does not digest itself.

If we give a similar meal to another man, adding to it a hydrophilic colloid of excellent hydration capacity, let us say $\frac{1}{2}$ to 1 ounce of gelatin, a definite change takes place in the contents, and if they are withdrawn for analysis, a gluey mass is recovered. It is not sour as would have been the contents of the stomach which did not contain gelatin; and on the contrary it does not show any acidity till the colloid is broken down. Under these conditions, digestion is quite generally distributed throughout the mass.

The gelatinous mass that results from the ingestion of a prepared hydrophilic colloid such as gelatin is formed more quickly than is the case when such raw foods as fruits and vegetables are used, which must first take up the digestive juices and then be partially digested before the mass develops. Raw meats apparently become gelatinous in less time than vegetables. But, as digestion proceeds, all raw foods become more or less gelatinous before liquification takes place. In case of cooked foods, gastric digestion is also directed toward the liquification of the stomach contents, but it is interfered with by the fact that the heat of cooking has precipitated the colloids.

CHOICE OF HYDROPHILIC COLLOID

The choice of hydrophilic colloids for this purpose is legion. Cactus juice and beet juice are both useful. They are considered excellent feed water compounds by engineers because they keep minerals in solution and prevent scale from forming in steam boilers. They are cheap but not refined. Mucin (2), colloidal aluminum hydroxide (3), agar, the edible sea weeds, and many proprietary preparations, which include certain of the silica jells, mucilaginous substances of vegetable origin, etc., are among colloids that may be used.

Each one of the above mentioned substances has one or more drawbacks. It is either too expensive, it produces toxic effects, it is not readily available, it is bad tasting, has insufficient hydration capacity, or it is indigestible. In my work I have chosen to use gelatin because it possesses none of the above disadvantages. It is non-toxic and has a good hydration capacity. It can be purchased at a reasonable price at any grocery or drug store. It is readily available. It can be served in many tasty ways. One can get it at any hotel or restaurant. It is completely digested. Should a hydrophilic colloid with bulk be needed, an indigestible colloid such as agar may be added.

SELECTION AND PREPARATION OF GELATIN

Just as there are grades of gasoline and flour, so are there grades of gelatin. Roughly in the competitive market the grade and price correspond. Gelatin may be made either by an acid or an alkaline process, and any of the poorer grades of commercial gelatins are either alkaline or acid to taste. The best gelatins are neutral. Gelatin may be bought in sheets, or in granulated form. The latter is more readily soluble. In this discussion it is the plain, unflavored and unsweetened gelatins to which we refer.

When one is to choose between two neutral gelatins of different grades, their adhesive properties serve as the best guide. To test this stickiness, take weighed

samples and place them in different containers of the same shape and size. Add to each weighed sample of gelatin an equal amount of cold water, and allow it to expand for five minutes. The containers with the samples of gelatin to be compared, are immersed to the same depth in boiling water and allowed to remain there until all the gelatin is dissolved. Then remove from the water and allow the mass to stand five minutes to cool. Take in turn a definite amount of each sample between the thumb and forefinger, and compare their stickiness. Wash and dry the hands carefully after testing one sample before testing the next. Though this method is rough, it is accurate enough and one will be surprised to find the difference shown by different samples of gelatin.

PREPARATION OF GELATIN

Gelatin may be served to the patient in many ways. It may be beaten up with an ice-cream-malted milk. Prepared in this way it is somewhat granular. It may be taken from a spoon, dry, and washed down with a liquid, although this is usually a very sticky procedure. It may be mixed with dry or cooked cereals, with vegetables, or many other foods. In my experience, the most satisfactory way to use it is to first dissolve it, by mixing it with cold water allowing it to stand in hot water until dissolved and then adding water and flavoring to make it the proper consistency and to improve its taste. It should be stirred while heating to mix it thoroughly. It may be made in concentrated form and added to soup or bouillon or made into a drink flavored to suit. Often a satisfactory method is to add stock solution made from the unflavored preparation to a little fruit flavored gelatin already sweetened. Cold dishes using the amount of gelatin recommended are too tough to eat. It must be remembered that if it is allowed to dry and adhere to cups and glasses it may break them by the contraction.

AMOUNT OF GELATIN

The amount of gelatin to be prescribed varies with the type of diet used and the purpose for which it is intended. If used in connection with a modified Sippy milk and cream diet using hourly feedings, from 7 a. m. to 7 p. m., gelatin, a dram to the feeding, may be added to the milk to take the place of the alkaline powders. For use with regular meals, $\frac{1}{2}$ to 1 ounce usually suffices for the adult. This is enough to make from two to four pints of dessert.

CLINICAL APPLICATION

The use of a hydrophilic colloid in the dietetic treatment of gastric complaints is frequently sufficient in itself to rectify what are apparently serious conditions. Gelatin may be used in conjunction with almost any diet that the clinician feels is indicated. Its colloidal properties aid the digestion of many foods which cause the patient to suffer from "sour stomach." Even foods to which individuals may be definitely sensitive as proven by the leucopenic index, and elimination diets, frequently may be tolerated with slight discomfort or none at all if gelatin is made a part of the diet. The favorable effect on digestion in the upper portion of the gastro-intestinal tract frequently leads to improvement in patients suffering from spastic colitis. The necessity for pureeing foods may not be found if hydrophilic colloids are added. Even

raw vegetables, green salads and fruits which are usually taboo may often be given to these patients with impunity after a short time.

A hydrophilic colloid diet will often give marked relief in the syndrome of slow digestion, gas formation, relaxed cardia and heartburn in which the burning is due to organic acids instead of an excess of the normal hydrochloric acid which frequently accompanies chronic inflammatory diseases affecting such organs as the heart, lungs, gall bladder and appendix. Here again the colloid may be used either in connection with the patient's regular food or with whatever diet the physician feels is best fitted for the patient.

In children who present problems of growth and development and those who show symptoms of allergy in the bowel, the hydrophilic colloid proves to be of great value. One usually prefers to use it in conjunction with a diet designed for the child's general up-building, although the addition of the colloid to the usual diet may be all that is necessary.

The patient with gastric atony or nervous indigestion who complains of heartburn and vomiting four or five hours after eating is often helped. There is apparently a lessening of the emptying time of the stomach and an improvement in gastric tone. A strict dietary regimen is not as necessary when the colloid is used.

Alcoholic gastritis presents a problem which the stewards of country clubs usually solve with their cannibal sandwiches of raw beef on rye bread. The effect is produced by the hydrophilic colloid of the beef. Gastric lavage, some pill or hot soda water have usually sufficed for the physician. The steward who uses the raw meat sandwich probably never heard of hydrophilic colloids yet he and his kind have handed on from father to son the knowledge that raw beef will meet the condition better than any other remedy. A tasty gelatin drink gives relief and allows the patient to avoid the raw meat which is usually distasteful to his squeamish sensibilities.

Gastritis in other forms can be relieved by the use of milk added to a suitable amount of hot gelatin concentrate, beaten thoroughly and taken before coagulation or setting.

While gastric hemorrhage requires special dietary supervision, that particular type with low acid and no demonstrable ulcer may be treated by substituting gelatin for the alkaline powders of the Sippy diet. The gelatin is given with the milk, and not between feedings. The milk, in order to have the greatest potency of vital elements, should be a green pasture raw milk. As was formerly pointed out by me (4) Pasteurization destroys some of the vital elements of milk. It also materially alters its colloids.

The true gastric or duodenal ulcer patient is of a different type and while some patients, as just mentioned, are frequently included under the general heading of gastric ulcer, they have no ulcer. When gastric ulcer with erosion demonstrable by X-ray is present, an increased gastric acidity is usually present. Formerly, attempts were made to reduce the hyperacidity chemically by the alkaline powders. Of late years, colloids too numerous to mention, such as

mucin, colloidal aluminum hydroxide and powdered okra, having different degrees of hydration capacity, have come into use. Absorption of gastric content by the colloidal mass rather than neutralization is the fundamental aim underlying these treatments. Absorption by the colloids of milk and cream, too, plays a large part in the Sippy diet. Therefore, in substituting gelatin for any of these excellent colloids, such as mucin, one is merely changing the nature of the colloid by replacing an indigestible colloid by a digestible one and also inserting an item of common household usage for an expensive preparation.

The dietary regimen to be followed with these patients depends largely upon the convictions of the practitioner. It usually has been my practice to follow a modified Sippy regimen, eliminating the alkalinizing agents and using gelatin instead.

DISCUSSION

Hydrophilic colloids have a very wide application in the field of dietetics provided a sufficient amount of an article of the proper quality is used. In reference to gelatin, which is discussed in this paper as being one of the most available products, we recognize that we are also dealing with a preparation which is a source of glycine, which, as shown by Brand, et al (5), is a muscle and tissue builder and an energizer of first importance; and that because of these properties it may play a very important role in certain of the chronic illnesses; nevertheless, its physiochemical properties seem to be the factors of most importance in the immediate problems of digestion. Gelatin is largely digested before it leaves the stomach, yet it has a profound effect on the entire gastro-intestinal tract. Exactly why this should be true is somewhat puzzling at first. However, if we consider the effect of unusual irritation upon the nerves of the gastro-intestinal canal, it is rational to think that a less violent and more nearly "normal" digestion above might quiet the activity of the otherwise hyperactive gut. Inasmuch as the same foods which formerly produced irritation may frequently be continued without harm when gelatin is used, the relief to nerve irritation seems to offer a logical explanation. Whether the change, in the lower gastro-intestinal tract, is due to the effect of the gelatin itself, or to a more complete digestion taking place along the entire tract due to physiochemical alteration is not clear.

Both factors are probably important. There is undoubtedly a better assimilation of food as is indicated by the general improvement which takes place in underdeveloped children without following so closely the carefully planned maintenance diets which are so often prescribed. Undernourished adults also respond with increased weight and strength without adding to the total calories of their diet.

SUMMARY

1. Hydrophilic colloids bring about conditions in the stomach during digestion which approach those resulting from the consumption of foods in their natural state.

2. Hydrophilic colloids lessen gastric irritation by

absorbing the digestive secretions of the stomach so that digestion takes place within a mass of food.

3. Gelatin, because of its availability, relatively low cost, non-toxicity, adaptability as an item of dietary and its thorough digestibility becomes an admirable hydrophilic colloid for dietary usage.

4. The amount of gelatin to be used in a given case depends on the patient's needs, but it must be of good quality and sufficient in amount.

5. It has a wide range of usefulness in gastro-

intestinal ailments ranging from the atonic conditions met in the chronic invalid to the irritating condition presented in gastric ulcer.

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The Biliary Tract Lesion of Duodenal Ulcer*

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DUODENO-BILIARY drainage, since its development by Lyon, has been used as a clinical pathological procedure almost exclusively for the diagnosis of cholecystitis and cholelithiasis. This restriction of the point of view has resulted in a failure to appreciate the usefulness of the procedure in the diagnosis of duodenal ulcer and its associated biliary tract lesions, except in a very limited way.

Because of diagnostic inconsistencies and uncertainties encountered in the interpretation of duodeno-biliary drainage alone, or of fractional gastric analysis alone, because of conflicting cholecystographic findings, and—not least—because of the occasional surgical removal of apparently anatomically normal gall bladders, we have undertaken the performance of duodeno-biliary drainage immediately followed by a complete physiologic fractional gastric analysis on all patients presenting gastric symptoms, who are referred to this laboratory for either of these tests.

The technic consists of: (1) aspiration of the fast-ing gastric contents; (2) passage of the duodenal tube into the duodenal zone; (3) stimulation of the biliary tract by the instillation of olive oil; (4) fractioning of the bile flow so as to obtain the most concentrated bile delivered during the gall bladder response, and at least two identical fractions of liver bile after the gall bladder flow has definitely ended; (5) prolongation of the drainage in order to obtain late sediments, and especially red mucus; (6) withdrawal of the tube to the gastric zone for a two-hour, seven-specimen, physiologic fractional gastric analysis after the ingestion of a simple Ewald test meal of tea and toast; and (7) complete aspiration of the stomach at the end of two hours.

On each bile fraction the quantitative bilirubin is determined, and all sediments are carefully examined microscopically. A search is made for red mucus, which usually may be found readily, floating on the surface of the fractions when present. The stomach specimens are titrated for free and total acidity with Töpfer's reagent and phenolphthalein, and the last specimen (complete aspiration) also is examined for red mucus.

This technic has proven remarkably satisfactory. Much of the success of the procedure may apparently be attributed to the use of olive oil instead of magnesium sulphate as the biliary stimulant. The former, immiscible with the duodenal contents and of low specific gravity, rises without disturbing sediments or the prevailing level of the duodenal fluid as it is instilled. The latter, an aqueous solution of high specific gravity, mixes freely with, and dilutes the duodenal fluid, causing sedimentary material to rise as floccules

TABLE I
Volumetric outputs of olive oil drainages

Time Interval	Number of Drainages	Maximum Output	Minimum Output	Average Output
82 drainages with gall bladder responses				
1-1½ hrs.	4	142 c.c.	60 c.c.	90 c.c.
2-2½ hrs.	34	500 c.c.	50 c.c.	201 c.c.
3-3½ hrs.	38	602 c.c.	87 c.c.	249 c.c.
4 hrs.	4	839 c.c.	388 c.c.	565 c.c.
5 hrs.	2	509 c.c.	274 c.c.	392 c.c.
46 drainages without gall bladder responses				
1-1½ hrs.	3	166 c.c.	61 c.c.	126 c.c.
2-2½ hrs.	18	405 c.c.	21 c.c.	201 c.c.
3-3½ hrs.	15	302 c.c.	74 c.c.	211 c.c.
4 hrs.	8	750 c.c.	195 c.c.	431 c.c.
5 hrs.	2	240 c.c.	230 c.c.	235 c.c.

high above the bucket of the tube, often, no doubt, to be washed up and over into the jejunum. An additional advantage of using olive oil is that digesting oil, in the form of palmitic acid crystals, may readily be identified microscopically as evidence of the presence of lipase from the pancreas.

Reflux of bile during the gastric analysis may usually be avoided by washing out the duodenum, the tube, and the antrum prior to the ingestion of the test meal.

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Duodenal ulcer has two commonly associated biliary tract lesions: (1) oleaginous cholangiosis (oleaginous catarrh of the bile ducts); and (2) an atonic gall bladder which fails to yield a shadow in the Graham test, and which often fails to respond to the first duodeno-biliary drainage. Since the bilirubin content of

siphonage, and often to be found in the stomach contents especially after a preliminary duodenal drainage, seems quite diagnostic in itself, and its constancy inspires the greatest respect for borderline free acid curves of the extragastric type derived from the gastric analysis when hyperchlorhydria is not

TABLE II
Grading of gall bladder responses

Maximum bilirubin content of normal liver bile 10 mgms./100 c.c.	
Grade I	11 to 15 mgms./100 c.c.
Grade II	16 to 25 mgms./100 c.c.
Grade III	26 to 45 mgms./100 c.c.
Grade IV	above 45 mgms./100 c.c.
Low grade I. responses may be doubtful. Abnormal liver bile may exhibit a bilirubin content above 10 mgms./100 c.c. when liver function is impaired, as in cholecystitis, or after cholecystectomy.	

normal liver bile, as obtained by duodeno-biliary drainage, does not exceed approximately 10 milligrams per 100 cubic centimeters, the absence of a gall bladder response is indicated by not finding a higher pigment level than this in any fraction. Such a finding will usually agree with a positive cholecystogram, provided that the cholecystogram was made prior to the drainage. Since even one oil drainage may stimulate an atonic gall bladder into subsequent resumption of its concentrating activity, a cholecystogram after a drainage in which no gall bladder response occurred, or a second biliary drainage, may be found to be normal. Oleaginous cholangiosis is readily diagnosed by the heavy sediments of yellow oleaginous substance and the coarse, fragmented, twisted mucus, with which it is often associated. This oleaginous material, clear and bright yellow under the microscope after it laves out from the mucus or forms by the coalescence of myriads of minute droplets, is rich in bilirubin. Oleaginous cholangiosis was first described by Lyon and Swalm in the *Journal of the American Medical Association*, March 17, 1928.

The diagnosis of duodenal ulcer is implied by the curves obtained in a physiologic fractional gastric analysis, and is sustained by the identification of red mucus. This red mucus, often obtained by duodenal

TABLE IV
Analysis of absence of gall bladder response

Diagnosis	Doubtful	Normal* liver bile	Abnormal** liver bile	Total
Catarrhal jaundice	0	3	1	4
Cholecystectomy	0	3	6	9
Duodenal actinomycosis	0	0	1	1
Surgical cholecystitis	1	7	4	12
Duodenal ulcer	1	18	0	19
Unclassified	0	2	0	2
*Bilirubin content not above 10 mgms./100 c.c.				
**Bilirubin content above 10 mgms./100 c.c.				

featured, and implies that acid dyskinesia as well as hyperchlorhydria is the outstanding characteristic of the duodenal ulcer diathesis. Achlorhydria is not an infrequent manifestation of acid dyskinesia. More frequently, however, the curves of acid dyskinesia, when hyperchlorhydria is absent, tend to be concave upward from the fasting specimen to the last fraction, or tend to show a sustained progressive increase in free hydrochloric acid throughout the entire interval. In general one can almost state that any curve which is not at its maximum (within normal limits) at the end of the first hour, and followed by a recession, may be regarded with suspicion. Usually there is found either a definite acid dyskinesia with hyperchlorhydria, or red mucus is obtained to establish the diagnosis.

No presumption is intended herein to make any statements about the interpretation of the results of fractional gastric analysis not already clearly defined by Rehfuess, the originator of the method, but it is felt that emphasis is necessary to point out the very material value of such interpretations. So called "normal" composite gastric analysis curves, as exhibited in many text books, are undoubtedly misleading, since many of the individuals tested may belong to the ulcer race with acid dyskinesia antedating their gastric symptoms.

From a clinical point of view this subject is open to a most interesting discussion. In typical repeated attacks of acute cholecystitis or biliary colic little diagnostic difficulty is encountered, and a positive cholecystogram or the exhibition of small calculi in a functioning gall bladder is an almost unnecessary formality prior to cholecystectomy. Biliary drainage offers little of diagnostic or therapeutic value in such cases. Contrary to prevailing opinion, the microscopy of biliary drainage is so meager in advanced chronic cholecystitis that it rarely yields any additional information. Formed calculi in a functioning gall bladder without sedimentary material in the form

TABLE III

Grades of gall bladder responses in 128 olive oil drainages

No response: normal liver bile*	32
No response: abnormal liver bile**	12
Doubtful	2
Grade I	11
Grade II	26
Grade III	23
Grade IV	22
*Bilirubin content not above 10 mgms./100 c.c.	
**Bilirubin content above 10 mgms./100 c.c.	

of gall paste or gall sand usually contribute nothing to the microscopy. Likewise a non-functioning gall bladder, although rich in tyrosin, cholesterol, or calcium bilirubinate as sedimentary material within its lumen, and severely inflamed in its wall, since it is usually sealed off from the biliary tract by obliteration

TABLE V

Nature and frequency of the biliary tract lesion of duodenal ulcer

Number of patients with duodenal ulcer	58
Number exhibiting red mucus	32
Number with non-functioning gall bladder at first drainage	18
Number with non-functioning gall bladder at first drainage, showing subsequent restoration of function	7
Number with normally functioning gall bladder	40
Grade I—response	4
Doubtful	1
Grade II—response	10
Grade III—response	14
Grade IV—response	11
Number exhibiting oleaginous cholangiosis	26
with functioning gall bladder	17
with non-functioning gall bladder	9
Number with other significant abnormal biliary microscopy	3
macrophages	2
cholesterol and calcium bilirubinate without calculi in gall bladder	1
Number exhibiting achlorhydria on first gastric analysis	2
Number exhibiting acid dyskinesia without hyperchlorhydria	12
Number exhibiting acid dyskinesia with hyperchlorhydria	45

of the cystic duct, can contribute nothing to the microscopy of biliary drainage. Patency of the cystic duct in such instances appears as a rare exception. When it is deemed expedient to perform a duodeno-biliary drainage in primary cholecystitis, the chief finding will be the absence of a definite gall bladder response when the bilirubin contents of the fractions are determined, although the occasional output of abnormal liver bile with an elevated bilirubin content may cause confusion when liver function impairment is a concurrent factor.

Since we have been conducting these studies it has been a rather common occurrence to find normal biliary tracts and normal gall bladder function in patients long believed to have chronic cholecystitis, but who exhibit the classical clinical pathological findings of duodenal ulcer. Several diagnoses of chronic appendicitis have paled in the light of similar findings.

It is a matter of considerable importance to the patient that duodenal ulcer not be diagnosed as chronic cholecystitis, for to the average physician the latter diagnosis at once connotes a taboo on fats. Lyon (2) has recently explained the physiologic necessity for the use of fats in the treatment of chronic cholecystitis to preserve the functional capacity of the gall bladder. The generous use of fats in the diet of the ulcer patient with an associated biliary tract lesion is

even more essential, since this type of involvement is often readily corrected in its early stages by such physiological stimulation of the gall bladder and bile ducts. Perhaps one of the chief reasons for the frequent success of the Sippy diet or its modifications is not simply that it provides concentrated nourishment in small frequent doses, but because it is a high fat diet which provides constant stimulation of the biliary tract.

A fat taboo to the ulcer patient often results in a sorry spectacle. The harassed patient, between Scylla and Charybdis, finds that there is not much he can eat which is not immediately prohibited by some solicitous member of his family interpreting his physician's instructions, or which does not in his own experience cause him pain and discomfort. Rarely is he aware that he is distressed by fats until so informed. On the other hand, the ulcer patient, correctly diagnosed, does fairly well so far as his incipient biliary lesion is concerned on the fats provided by a conventional ulcer diet.

The masking of the ulcer syndrome by the superimposed biliary syndrome, often characterized by belching and distressing nausea and vomiting, and not infrequently associated with a positive cholecystogram, is obviously one of the commonest sources of error in gastro-enterological diagnosis. Duodeno-biliary drainage coupled with physiological fractional gastric analysis is indeed a time-consuming procedure when properly performed, but it does replace speculation in many instances, and may serve to prevent the removal of anatomically normal gall bladders and to mitigate the fallacy of the fat taboo.

Studies so far completed would imply that duodenal ulcer is a very widely prevalent disease in individuals of both the leptosomic and the pyknic constitutions, manifested in modes often dissimilar to the well known ulcer syndrome, and may well be the most important predisposing lesion in the development of the intractable late cholecystopathies.

SUMMARY

The differential diagnosis between surgical cholecystitis and duodenal ulcer with an associated oleaginous catarrh of the bile ducts or transient cholecystostony can usually be made by the combination of duodeno-biliary drainage and fractional gastric analysis. Frank cholecystitis or biliary colic, requiring surgical intervention, rarely demand confirmatory studies when the syndrome is known to be classical. Borderline patients, however, with ulcer syndromes masked by a superimposed biliary syndrome require careful studies in order to prevent the non-beneficial removal of anatomically normal gall bladders or the injurious prohibition of fats in their diets.

The diagnosis of duodenal ulcer rests upon the demonstration of acid dyskinesia, with or without hyperchlorhydria, by physiological fractional gastric analysis, and the detection of red mucus from the duodenal or gastric zones. The diagnosis of the associated biliary tract lesion of duodenal ulcer rests upon the identification of oleaginous material, oleaginous mucus, or ~~colored, opalescent~~ fragmented mucus in abundance in the sediments from duodeno-biliary drainage, and on the demonstration of the initial absence of a gall bladder response restored to normal by repeated oil drainages or by an adequate fat diet.

Neglect of the biliary tract lesion of duodenal ulcer, and especially a fat restricted diet, may lead eventually to surgical cholecystitis.

Duodenal ulcer appears to be a widely prevalent disease in individuals of both leptosomic and pyknic types.

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DISCUSSION OF TABLES

Table I. Volumetric outputs of olive oil drainages.

This table merely shows the volumetric outputs of olive oil drainages during measured time intervals. No pertinent contrast is implied by comparison of those with and without gall bladder responses. Although the series is relatively small, a number of significant details, as demonstrated in this table and those that follow, have been thoroughly worked out.

Lyon finds that the yield of a satisfactory drainage

be considered to have occurred when, after the instillation of olive oil, more than 10 mgms./100 c.c. are found in one or more consecutive fractions, followed by fractions with levels not above this amount upon the cessation of the gall bladder flow. Fractioning is a simple matter of changing the receiving jars at arbitrary intervals, guided chiefly by the detection of changes in the color density of the outflowing bile. Even when the outflow appears continuously of the same color density it is advisable to change the jars at intervals, for occasionally a gall bladder response will not be apparent by observation alone, but may be detected by the quantitative bilirubin determinations.

In drainages yielding abnormal liver bile it is at times difficult to distinguish a low grade I response (11 to 12.5 mgms./100 c.c.) from abnormal liver bile. Frequently such doubt may be removed by continuing the drainage as long as possible to demonstrate the persisting high bilirubin level of abnormal liver bile and the lack of contrasting elevations in response to oil instillation. Cholecystography may occasionally be necessary under such circumstances. When the gall bladder is known to have been removed, a high bilirubin level is obviously indicative of abnormal liver bile. No evidence has yet been acquired that the ducts, even when dilated, have any concentrative capacity,

TABLE VI

Estimated average bilirubin outputs in milligrams per 24 hours
[Assuming output could continue at same rate as during drainage interval]

Group	Grade of gall bladder response				No gall bladder response	
	I*	II	III	IV	Normal* Liver Bile	Abnormal** Liver Bile
Duodenal ulcer	435 (3)†	265 (14)	310 (13)	551 (11)	109 (21)	—
Cholecystectomy	—	—	—	—	72 (1)	197 (4)
Catarrhal jaundice	208 (1)	238 (1)	350 (1)	760 (1)	150 (2)	417 (2)
Surgical cholecystitis	—	—	—	—	110 (6)	182 (4)
Duodenal Actinomyces (before cholecystectomy)	—	—	—	—	—	412 (1)
Duodenal Actinomyces (after cholecystectomy)	—	—	—	—	—	236 (2)
Unclassified	125 (6)	225 (10)	373 (9)	415 (9)	83 (2)	—

*Bilirubin content not above 10 mgms./100 c.c.

**Bilirubin content above 10 mgms./100 c.c.

†Figures in parentheses indicate number of drainages on which average is based.

should average 300 cubic centimeters in a three-hour interval when magnesium sulphate or peptone are used as the stimulants. Since a considerable portion of this amount may be accounted for by the diluent action of these stimulants, the outputs obtained with olive oil, as shown in this table, may be considered quite adequate in comparison. In computing these volumes all washings have been disregarded, and the top layers of olive oil are likewise not included.

The volume output during a given time interval is not always properly comparable with that of other time intervals, since occasionally a drainage will flow poorly or cease to flow, whereas others will flow so freely that they may have to be discontinued in the midst of the flow, or allowed to continue as long as the patient desires.

Table II. Grading of gall bladder responses.

The terms "grade" or "grading" as used herein do not imply pathology, but, on the contrary, the degree of normality in the sense of physiologic functional capacity on the part of the gall bladder. Upon fractioning the biliary outflow in a series of from four to eight or more receiving jars, and upon the determination of the bilirubin levels of the various fractions, a gall bladder response may

for the abnormal liver bile continues to flow long after sufficient volume has been obtained to evacuate the most sacculated biliary tree.

Since the gall bladder does not always empty completely in response to a single instillation of olive oil, a second rise in the bilirubin level immediately following a repeated instillation may be construed as a gall bladder response.

During the flow of the "B," or gall bladder fraction, liver bile also flows, causing a dilution of the gall bladder bile, so that the bilirubin level of the most concentrated fraction of this portion of the flow cannot be considered to represent the actual concentration existing in the gall bladder itself, but must be considered only as a relative value.

Table III. Grades of gall bladder response in 128 olive oil drainages.

This table demonstrates the relative infrequency of doubtful responses as well as the low incidence of grade I responses. Additional drainages carried out in the warm days of early summer, since the compilation of this table, have shown a rather marked increase in frequency of the very high grade IV responses. This observation may be merely coincidental, or it may imply that the light diet of

warm weather affords little stimulus to the average normal gall bladder, causing higher concentrations to occur.

Table IV. Analysis of the absence of gall bladder responses.

Herein are tabulated the clinical diagnoses associated with failure to obtain gall bladder responses in duodeno-biliary drainage.

Table V. Nature and frequency of the biliary tract lesion of duodenal ulcer.

In this table are tabulated a number of cases in which the diagnosis of duodenal ulcer has been satisfactorily established from a clinical point of view. Confirmatory

these 18 patients may develop severe cholecystopathy in time, although all are now reported doing well on ulcer management and an adequate fat diet.

It is not the intent of this paper to prove that all cases of severe cholecystitis requiring surgical intervention are the result of unrecognized duodenal ulcer, but the more critically one studies this phase of the question the more one is impressed by the fact that this does seem true in a surprisingly large number of such instances. Although this surgical group is not presented here, many of the patients comprising it have presented undeniable evidence of the existence of duodenal ulcer in addition to their pathological gall bladders, and in several the ultimate decision to perform a cholecystectomy matured rapidly following the institution of the fat-free diet.

Table VI. Estimated bilirubin outputs in milligrams per 24 hours.

The figures in this table represent the 24 hour outputs of bilirubin calculated from the amount of the pigment excreted during the measured time intervals of duodeno-biliary drainage. Naturally, when a gall bladder response occurs, the estimate will be appreciably in excess of the physiological 24 hour output, because of the contribution of the gall bladder contents, which is but a transitory factor. However, these figures do imply clearly the actuality of the gall bladder response as contrasted with the estimates obtained from the data on drainages in which the response is lacking.

It is also apparent that when abnormal liver bile is obtained the bilirubin outputs exceed those observed when normal liver bile is obtained. This phenomenon does not necessarily imply an overproduction of the pigment by the hemolytopoietic system, for it is also possible that oil stimulation may evacuate the lobules of a pigment-laden liver quite independently of any such factor as overproduction of the pigment at its source beyond the liver. To elaborate on this point a little further, the following extraordinary finding might well be mentioned. A patient finally found to have duodenal actinomyces had had over an interval of several years an ulcer syndrome, a gall bladder syndrome, an appendectomy, and a cholecystectomy. Neither of the two operations afforded much of any relief. The ray fungus was finally discovered in a duodeno-biliary drainage two years after the removal of a moderately pathological gall bladder. In this drainage the fractions comprising the first 100 cubic centimeters of bile exhibited bilirubin contents of 9 to 10 mgms./100 c.c. The following fractions, comprising another 100 cubic centimeters assayed 18 mgms./100 c.c., and the terminal fraction dropped to 6 mgms./100 c.c. If it were not known that this patient had had his gall bladder removed, these findings would be fairly typical of a delayed grade II gall bladder response. The fact that the first 100 cubic centimeters of bile was sufficient in volume to evacuate whatever might have been in the bile ducts, whether dilated or not, and exhibited a low bilirubin level, seems to imply that the subsequent 100 c.c. must have come from a pigment-laden liver which readily discharged its overload during the period of the drainage. Other explanations of this exceptional finding are theoretically quite admissible.

The 24 hour bilirubin outputs in the absence of a gall bladder response, as shown in this table are somewhat higher than the actual 24 hour outputs obtained by surgical choledochostomy reported in an earlier paper (3), and indicate that, although variable, the average is about 110 milligrams for a human adult.

CHART I

Quantitative bilirubin method for bile [As obtained by duodeno-biliary drainage]

REAGENTS: 1. Ehrlich's diazo reagent 2. 95 per cent ethyl alcohol 3. Cobaltous sulphate bilirubin standard [Same reagents as are used for serum bilirubin]	
PROCEDURE: 1. Place 1 c.c. of bile in common graduated centrifuge tube 2. Add 1.5 c.c. Ehrlich's diazo reagent 3. Fill to 10 c.c. mark with 95 per cent ethyl alcohol and shake (gives clear ruby red solution of azobilirubin) 4. Place some of azobilirubin solution in cup of Duboseq colorimeter and match with cobaltous sulphate standard. Set standard at 5 millimeters. Standard is equivalent to 0.5 milligrams bilirubin per 100 c.c.	
CALCULATION: Bilirubin content in milligrams per 100 c.c.	
$\frac{\text{Reading of standard}}{\text{Reading of unknown}} \times \text{dilution factor} \times (0.5)$	
or	
$\frac{25}{\text{Reading of unknown}}$	

X-ray findings have been reported in many of these, and in each case follow-up histories have substantiated the original findings with a very reasonable degree of accuracy.

Red mucus is usually identified by careful inspection of the duodenal or gastric specimens, and is generally found floating on or near their surfaces. Grossly and under the microscope its color is red or reddish brown. It appears to consist chiefly of a decomposition product of hemoglobin. Sometimes it is manifest as light brownish shreds, difficult to identify grossly, but which stand out prominently by their blue-green color in the benzidine test when the surrounding fluid shows no evidence of the presence of occult blood. It gradually loses its distinctive coloration on standing.

Among the 18 patients exhibiting non-functioning gall bladders only one is known to have undergone cholecystectomy, and then, after the removal of an anatomically normal gall bladder, symptoms persisted until ulcer therapy was instituted. It is conceivable that a number of

Gastric Acidity in Chicks with Experimental Gastric Ulcers*

By

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EROSIONS of the gizzard were first described by Dam in 1929 in conjunction with a hemorrhagic dietary deficiency disease in chicks (1), now known as chicken hemophilia. More recently, Almquist and Stokstad (2) have shown that the erosive lesions in the muscular part of the chick's stomach are independent of the hemorrhagic syndrome and can almost constantly be produced by a basal fish meal diet containing the known vitamins, but devoid of alfalfa and grain. The gastric lesions appear in the early weeks of life when the chicks are placed on this diet from the time they are hatched, and may be completely prevented by addition of adequate amounts of alfalfa and hempseed, their extracts, and by a number of other substances. His work also suggests that well established lesions may be cleared up by adding a rich supply of the "anti-gizzard erosion factor."

These same gastric erosions were observed by the author while studying fowl hemophilia (3). Over 200 stomachs have now been examined which show characteristic changes. The most striking of these lesions are single, but they are more commonly multiple, varying from a millimeter to a centimeter in diameter and grossly resembling human gastric ulcers (Fig. 1).



Fig. 1. Gastric ulcers in chicks. Circles indicate location of ulcers. A. Superficial hemorrhagic ulcers. B. Large penetrating ulcer.

Although they are often superficial and have previously been designated as erosions they may involve underlying structures and become chronic. It appears justifiable in accordance with Hurst's view (4), to call all these lesions gastric ulcers. The histo-pathology of these ulcers will be described elsewhere (5). One is struck by the analogy of this disease in chickens to that occurring in humans. The lesions are in the

muscular portion or gizzard which corresponds to the pyloric region of the stomach in man (6), and very rarely occur in the upper glandular portion of the stomach. They are most common where the acid glandular secretion first strikes the distal non-acid producing mucosa which is covered by a firm mucoid secretion in the chickens. They occur in a stomach where muscular activity is normally marked (7). There is gross and microscopic evidence of localized gastritis, and the entire fundus may be involved. Another characteristic and a constant finding in chicks on this basal diet is a loss of muscle substance and tone of the stomach which may reduce its weight to one-half of the expected normal. This occurs whether ulceration is present or not.

With these findings in mind one is naturally curious as to the secretion of acid in the stomach of the chicken. Although it is stated that acid and pepsin are secreted (8), no studies of gastric acidity by modern clinical methods could be found. Consequently a satisfactory technique has been worked out, it having been determined by autopsy studies, that acid is only produced in the glandular portion or fundus and that the secretion of the muscular or pyloric portion is always alkaline.

METHOD OF GASTRIC ANALYSIS

It was found necessary to use an anaesthetic and sodium pentobarbital (Nembutal) was chosen as the most satisfactory one. It was administered intramuscularly in a dose of 48 to 60 mgs. per kilo of body weight. Chicks varied somewhat in their response, the smaller dose not producing sufficient drowsiness, while the larger dose produced exitus in five instances before the test could be completed. Occasionally a second small dose of pentobarbital would have to be given if the first dose was too small. Ideally administering 54 mgs. to a one kilo bird would produce deep sleep for one to three or four hours, permitting very satisfactory study. For intubation, a small rubber catheter perforated at the tip was introduced into the gastric fundus. Numbers 12 and 14 French urethral catheters were found most serviceable for this purpose, although they were barely of sufficient length for the older birds. Their introduction into the stomach proved somewhat difficult at first due to their tendency to curl up in the crop. This difficulty could usually be overcome by turning the bird on its back and stretching out its neck; with practice the procedure became relatively simple. The catheter was fastened to the beak by adhesive to prevent regurgitation of the tube.

The birds were kept fasting 12 to 24 hours, but were usually allowed water freely. Although the fasting contents of autopsied birds almost invariably shows the absence of free HCl, during life free acid is usually present. Routinely the fasting contents were aspi-

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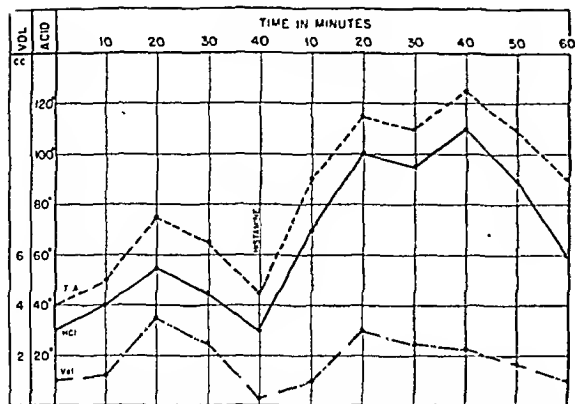


Fig. 2. Gastric acidity and volume curves under basal conditions and after histamine injection in a seven months old chicken.

rated over a 10 to 15 minute interval and then histamine was administered intramuscularly in a dose of 0.01 mgs. to birds weighing less than 1 kilo and 0.02 mgs. to birds of 1 kilogram and over. This is comparable to the dosage for man. The histamine solution was freshly made up each day. After the injection of histamine, specimens of the gastric contents were removed at 10 minute intervals for one hour, and their volume, gross characteristics, and free and total acidity recorded. If the stomach was well emptied the gastric juice was opalescent and usually yellowish or greenish due to bile. Occasionally after 40 to 50 minutes there would be an insufficient amount of secretion to examine. Free and total acidity were titrated in the usual manner with Topfer's reagent and phenolphthalein, except smaller volumes of gastric

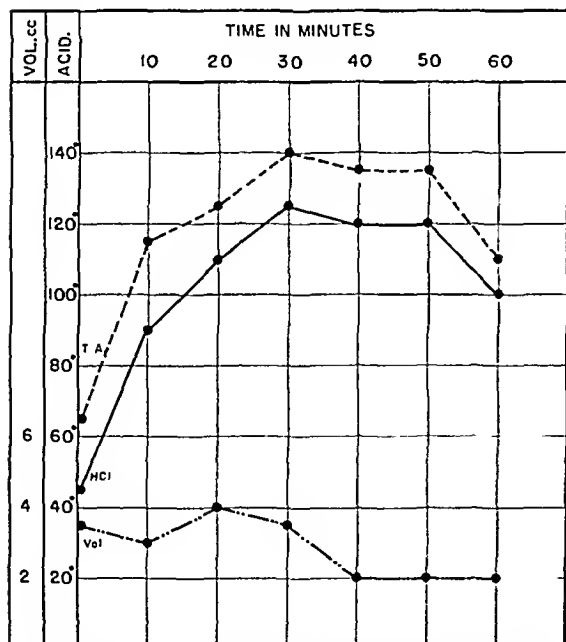


Fig. 3. Gastric acidity and volume curves after injection of histamine in a four months old chicken with a large gastric ulcer.

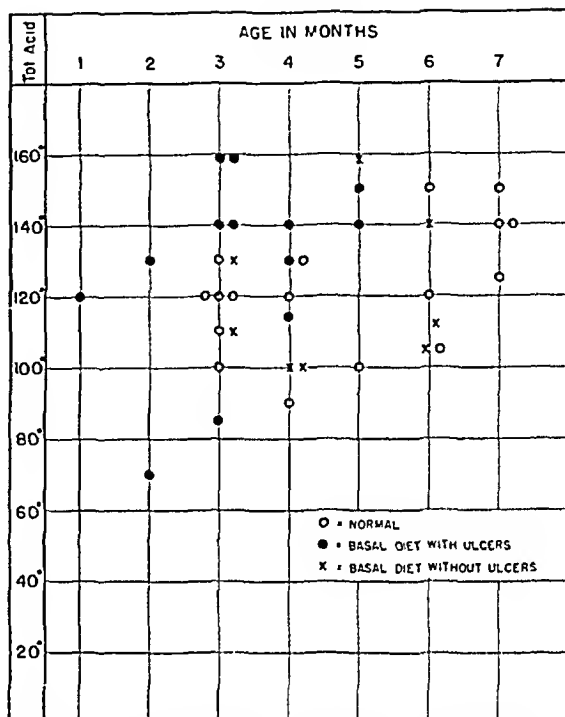


Fig. 4. Highest total gastric acidity recorded by months in thirty-eight chickens.

juice had to be employed, usually 1 or 2 e.e. Consequently, 0.01 normal sodium hydroxide was used instead of 0.1 normal. No routine tests were made for pepsin. The birds on the basal diet and most of the normal birds were autopsied after the gastric analysis to determine the presence or absence of gastric lesions.

Gastric secretory findings are surprisingly constant. Repeated studies in three birds showed essentially the same results. Fig. 2 illustrates the acid and volume values for the normal chick. In this experiment the basal secretion was studied at 10 minute intervals for 40 minutes before the injection of histamine. A temporary increase in free and total acidity to 55° and 75° occurred and the 10 minute volume rose to 3.5 c.c. with a subsequent marked drop. After histamine injection the free HCl rose to 110° and the total acidity to 125° in the fourth aspiration and then fell. The 10 minute volume of secretion rose to 3 c.c. and gradually fell to the initial figure. Fig. 3 illustrates the results of a routine gastric analysis in a chick with a large gastric ulcer. The findings are similar except higher acid values were reached and the volume of gastric contents obtained was somewhat greater. The striking similarity of these gastric analysis curves to those obtained on the human patient are obvious.

Gastric acidity studies were carried out on 38 white leghorn chicks† varying in age from 3½ weeks to 7 months. These birds were divided into three groups; those which were considered normal, those on the basal diet which showed ulcerative gastric lesions, and those on the basal diet which showed gastric atony of the gizzard, but no pronounced lesions of its lining.

There were 17 birds in the normal group which were

†I am indebted to Poehlmann's Hatchery in Petaluma, California, for donating all the birds studied.

on a liberal grain and alfalfa diet and which were kept in a large roofed pen out-of-doors. They varied in age from 3 to 7 months. The highest total acidity findings are recorded by age in Fig. 4. The average total acidity for the group was 121.8°, with a variation between 90° and 150°. The acidity was above the average in 7 birds or 41.2%. Sixty minute total volume studies were available in 20 normal birds, an additional three having been added in which exact acid values were not recorded. The average amount of gastric contents obtained in these birds in one hour was 14.1 c.c. with a variation between 8.1 e.e. and 26.3 c.c. The average age for these chicks was 4.6 months.

There were 13 birds in the second or ulcer group and they varied in age from 3½ weeks to 5 months.

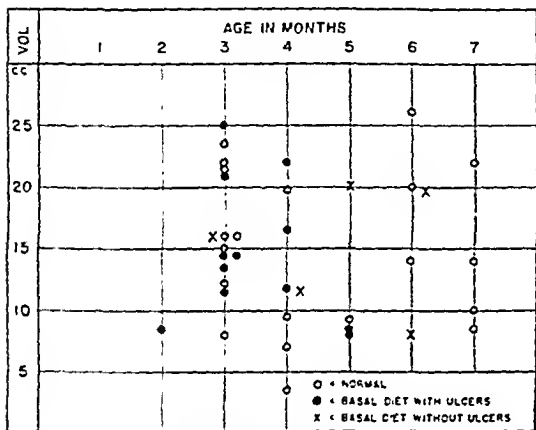


Fig. 5. Total hourly volume of gastric contents after histamine injection recorded by months in thirty-seven chickens.

Their experimental basal diet consisted of fish meal 17.5%, brewer's yeast 7.5%, sodium chloride 1%, cod liver oil 1%, and rice flour 73%. These birds were kept in doors in small pens with boarded floors, or cages with screened floors. The acidity values are also recorded in Fig. 4 for comparison with the normals. The average total acidity for this group was 138.6° with a variation between 115° and 160°. The acidity was above the normal averages in the nine instances or 81.8%. Two birds with low acid values are shown in Fig. 4 which are omitted from these averages as they died before their gastric secretory studies could be completed. Volume studies for the group are recorded in Fig. 5. The average of 12 birds for one hour was 15.4 c.c. with a variation between 8.0 e.e. and 25.0 e.e. Sixty minute volume studies could not be completed in one of this group. The average age for the group was 3.5 months.

There were 8 birds in the third group. They received the same experimental diet as the previous group, but failed to show ulcerative lesions at the time of autopsy. The age of these birds was from 3 to six months.

The acidity values shown in Fig. 4 average 114.3° with a variation between 105° and 140°. Two birds or 25% showed acid values above the average normal. The volume of secretion for 5 birds is recorded in Fig.

5 in the same fashion as in the previous groups. The average volume for one hour was 15.0 c.c. with a variation between 7.9 e.e. and 20 c.c. The average age of these birds was 4.8 months.

A comparative analysis of the gastric acidity values for the normal and experimental groups of chickens suggests that chickens with experimental gastric ulcers due to dietary deficiency secrete gastric juice of a higher acid titer than normal birds, and may also secrete larger volumes of this juice. On the average the chicks with ulcers secreted 16.8° higher acid than the normals, and 24.3° higher than the experimental group without ulcers. Or, it may also be stated that only two-fifths of the normal birds had acid values above the average, while the birds with ulcers had four-fifths of their group above the average normal. In the third group, only one-fourth of the chicks had acid volumes above the average. If any variation of acidity with the age of the chick by months can be deduced from Fig. 4, it would seem that the older birds in this series tend to secrete more highly acid juice. As the majority of chicks with ulcers are in the younger age groups, it would make the increased acidity for this group all the more convincing. Comparison of the experimental groups with and without ulcer make the difference even more pronounced particularly as it has been noted that after the first four or eight weeks, chicks on an ulcer producing diet are less likely to show ulcers. Gastric analysis is difficult in chicks under one month of age and no adult chickens have been included in this study, consequently, the relationship of gastric acidity to the age of the developing chick in months and the adult chicken in years must await more extended observations. It is noteworthy that achlorhydria was not encountered in this series of young birds, even though gastritis was pronounced in some cases.

Chicks secrete large volumes of gastric juice as Fig. 5 shows. The ten minute volumes have reached as high as 8 e.c. and the total hour volumes equalled 2% of their total body weight. Although the ulcer group averaged only 1 c.c. more than the normal group per hour, the majority were much smaller birds and averaged a month younger in age than the normals. As it is reasonable to assume that in a large number of observations the relatively small stomach of a young chick will not secrete as large a volume of juice as that of an almost mature bird, this difference is probably real rather than apparent, and indicates that chicks with ulcers have hypersecretion.

As human patients who develop gastric ulcers may show a lower acidity when they are free of the symptoms and signs of ulcer, than when they are ill, the tendency in chicks without ulcers to show a lower acidity than those chicks with ulcers may be comparable. A plausible explanation of this difference in acidity would be that the normal balance between acid and base components of the total gastric secretion is interfered with when the diet is deficient and that instead of there being an excessive amount of acid secreted there is in reality too little alkaline secretion produced. The disorder might then be termed a hypo-alkalinity, rather than a hyperacidity. It is in keeping with the known fact that other factors than hyperacidity are important in producing gastric ulceration, and these chick experiments strongly suggest that

one of these factors, and a major one, is a dietary deficiency of an as yet unidentified substance necessary to the local resistance of the gastric mucosa.

CONCLUSIONS

1. Experimental gastric ulcers may readily be produced in chicks on a deficient diet.

2. Gastric acidity in chickens following histamine injection is comparable to that found in man.

3. Chickens with gastric ulcers have hyperacidity.

4. The increased acidity in chicks with ulcers over those without ulcers suggests that it is a result of whatever causes the lesions and not a direct cause in itself.

5. The cause of the ulcers and the hyperacidity is apparently the lack of a dietary factor which has a specific effect on the resistance of the gastric mucosa.

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Some Recent Advances in the Physiology of Gastric Secretion*

By

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PHYSIOLOGICAL experiment in the field of gastroenterology during the last few years has indisputably shown that the digestive glands are organs of compound structure, composed of different sets of epithelial cells, whose activity is regulated—i.e. stimulated or inhibited—by different nerves or by various hormonal or chemical agents. The secretory work of a gland therefore is not regulated as a whole, but the final product of this activity, namely the glandular secretion, and in particular its composition are dependent on the participation of various mechanisms—nervous or humoral—which stimulate different parts of the gland. It may thus be concluded that the *quantitative* changes which under physiological conditions occur in some of the digestive juices, produced by glands of compound structure, in response to various stimuli are due to unequal *quantitative* activity of different groups of epithelial cells in these glands (Babkin, 1931, 1934). This theory is not inconsistent with two well established facts, *viz.*:

(1) The influence—positive or negative—that one nervous or humoral stimulus, which affects predominantly one group of glandular cells, may exert on another stimulus, which controls some other group of cells, and *vice versa*. The best example of this is the so-called “augmented salivary secretion,” where the preliminary stimulation of a parasympathetic nerve increases the effect produced by subsequent stimulation of the sympathetic nerve.

(2) The alternation in the volume and composition of the secretion that may be brought about by a change in the intensity of stimulation applied to a nerve which acts on only one group of secretory cells. Many examples of this could be quoted. For instance, it is well known that, when the chorda tympani is stimulated with an electrical current of a certain intensity and the intensity of the current is then raised, not only is the volume of the submaxillary secretion

increased, but the saliva is enriched with organic colloidal material and inorganic salts. Again, under vagal stimulation an increase in the volume of the gastric and pancreatic secretions and in their respective enzyme contents is to be noted as a rule on any increase in the strength of the current applied to the vagus nerve. The probable cause of this phenomenon is that the glandular cells which supply the digestive juices with organic colloidal material and enzymes are subject not to the “all or none” law but to some other law (Babkin, 1931; Mansfeld, Hecht and Kovács, 1931).

With particular reference to the gastric mucosa it should be mentioned that, in addition to the fact that it is composed of different structural elements—surface epithelium cells, mucous cells of the neck, peptic cells and parietal cells—the relative numbers of these cells vary in different parts of the fundus and corpus mucosa (Aschoff, 1923). Thus what one may term the “functional topography” of the gastric mucosa must not be overlooked in considering the various ailments of the stomach.

Furthermore, in the region of the lesser curvature (which includes the so-called “Magenstrasse”) the mucous membrane is much thinner than in the fundus and the corpus of the stomach, and it should be noted that this region and also the pyloric region are under much more effective nervous control than the rest of the organ. Thus, according to Schabadash (1930), a section of the gastric wall with a surface of 4 sq. cm. will on the average contain:

In the region of the fundus, 80 to 200 nerve cells.

In the region of the corpus, 250 to 320 nerve cells.

In the region of the pylorus and lesser curvature, 320 to 450 nerve cells. Presumably on account of the abundant nerve supply the secretory activity of a pouch constructed in the region of the lesser curvature is distinctly more under the control of the vagal innervation and less under hormonal control than that of a pouch formed from the gastric wall at the greater curvature (Alley, 1933; Davidov, 1935).

*From the Department of Physiology, McGill University, Montreal, Canada.
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With these preliminary data in mind we shall discuss some of the problems relating to the function of the gastric mucosa in normal and abnormal conditions. As a result of our own experiments on the dog and cat and on man, and taking into consideration the data obtained by other investigators, we may draw the following conclusions.

(1) It is well known that, while gastric secretion is at its height, there is very little variation in the acidity of the juice and in the concentration of total and of neutral chloride. Towards the end of the secretory period the acidity usually becomes somewhat less, and the concentration of total chloride diminishes, while that of the neutral chloride increases. Several theories have been suggested in explanation of this phenomenon.

According to Pavlov (1910), the small amount of gastric juice of constant acidity which is produced during this period of secretion is neutralized by the alkaline mucus of the surface epithelium. This view has recently been upheld by Webster (1929) and by Bolton and Goodhart (1931). In addition to the neutralizing influence of the gastric mucus, Hollander (1934, 1936) emphasizes the importance of the neutralizing effect of the "alkaline component"—a fluid secreted by cellular groups of the gastric glands other than the parietal cells, which latter always produce a secretion of constant acidity. Hollander supposes that the "alkaline component" is a mixture (isotonic with blood) consisting of neutral chloride and various buffer salts, chiefly bicarbonate; as such it may contain only 350 to 380 mg. per cent (99 to 108 m.eq. per liter) of Cl, whereas the Cl values of the acid gastric juice very often attain a level of 575 to 585 mg. per cent or more (up to 170 m.eq. per liter). He believes that the concentration of total chloride in the gastric juice is not constant but increases with the increase of the acidity. The same relations between the total chloride and the acidity were found by Wein and Frisk (1936) to exist in human gastric juice. Since, as we shall see later, the volume of the "alkaline compound" is small, and its alkalinity very moderate, its effect becomes noticeable only when the secretion of acid has greatly diminished, and results in an increase in the concentration of neutral chloride in the juice. Unfortunately data concerning the actual composition of the "alkaline compound" are lacking. However, a few facts are known regarding the composition of gastric mucus, the source of which is the surface epithelium and perhaps also to some extent the mucous (chief) cells of the neck. According to Bolton and Goodhart (1931), the gastric mucus of the cat under ordinary conditions contains from 0.28 to 0.36 per cent of inorganic chloride. Mucus collected from the entire stomach of a dog by Webster (Ph.D. Thesis, McGill University, 1933—unpublished) contained 471 mg. per cent of total chloride; its alkalinity amounted to 16.8 m.eq. per liter. Gastric mucous secretion obtained on stimulation of the splanchnic nerves in the cat (Baxter, 1934) possessed an alkalinity of from 11.2 to 14.0 m.eq. per liter and a total chloride content of 462 to 510 mg. per cent. The chloride content of gastric mucus in humans averages 100 m.eq. per liter (Wein and Frisk, 1936). It would be of great assistance to the physiologists in determining the composition of the gastric secretion minus the hydrochloric acid, if some of the clinical investigators would analyze the secretion produced by the gastric glands in

cases of achylia gastrica where no hydrochloric acid is being secreted but pepsin is still present in the juice.

According to the above theory, the composition of the principal components of the secretions of various cellular groups of the gastric glands is constant. On the other hand, Rosemann (1907, 1920) and his followers believe that the composition of the gastric juice may vary. In their view the concentration of total chloride in the gastric juice is practically constant, but the intensity of the stimulus determines the distribution of chloride between the hydrochloric acid and the neutral chloride. The stronger the stimulus, the more chloride will be present in the juice in the form of hydrochloric acid and the less in the form of neutral chloride.

It seemed to me (Babkin, 1929) that the variations in the acidity of the gastric juice could be accounted for by abnormally increased secretion of the "chief (or mucous) cells of the neck." These cells are present in the gastric tubules in considerable numbers; they gradually become more numerous towards the pyloric end of the stomach, the number of peptic cells correspondingly diminishing. Therefore the admixture of the secretion of the "chief cells of the neck" to the gastric juice must be substantial. It is quite possible that the glucoprotein present in the gastric juice in soluble form (so-called "dissolved mucin"—Webster and Komarov, 1932; Komarov, 1935) is secreted partly by the "chief (or mucous) cells of the neck" and partly by the peptic cells. However, very little is known as to the conditions governing their activity under various physiological and especially under pathological circumstances. Of the clinicians MacLagan (1934) considers it possible that in the human gastric glands these cells secrete a fluid containing neutral chloride.

All the above theories regarding the variations in the acidity of the gastric juice are based almost exclusively on data obtained from the investigation of healthy animals. The variations in the composition of the gastric juice in such cases are not at all great and this makes it difficult for the advocates of one theory or another to offer convincing proof of the correctness of their surmises. Thus the gastric glands of the dog, even when stimulated to activity by such different agents as vagal impulses and histamine, produce a juice with an almost maximal content of hydrochloric acid. We (Babkin, 1931; Toby, 1936) have shown that under these circumstances the parietal cells are able to secrete almost all the chloride of the juice in the form of hydrochloric acid. But does this mean that the parietal cells are under all circumstances able to concentrate the chloride from the blood and to combine almost all of it with hydrogen-ions? It seems to me that the best approach to a solution of this problem—a problem which has occupied the attention of investigators for more than half a century—would be by careful study of clinical cases and by special experiments on animals in which certain pathological conditions of the gastric secretory function have been reproduced. It might be expected that under the influence of a pathological process some phases of glandular activity would become exaggerated, others diminished or even perverted, so that the entire functional capacity of a particular group of secretory cells would be revealed.

(2) In normal canine gastric juice, secreted under

either nervous (sham-feeding) or histamine stimulation, the greatest part of the fluid and of the total chloride is produced by the parietal cells. This is evident from the data obtained by Miss Toby (1936), who showed that the concentrations of total chloride in "sham-feeding" juice and "histamine" juice are practically equal and are maximal in both secretions. Whereas the "sham-feeding" juice is extremely rich in organic material (*e.g.* pepsin, mucin), the "histamine" gastric juice is almost completely devoid of it. If the organic material produced by the peptic and mucoid cells were secreted along with a considerable amount of fluid, the total chloride of the "sham-feeding" juice would have to be much lower than that of the "histamine" juice, because in the secretion from these cells the chloride concentration is presumably much less than in the parietal secretion. However, this is not the case. Therefore it may be assumed that under normal conditions the peptic and mucoid cells of the dog's gastric mucosa discharge their colloidal organic material with a minimal amount of fluid. This is in agreement with the well known fact (*cf.* Katsch, 1926, p. 447; Bloomfield and Pollard, 1933, p. 41) that in some cases of achylia gastrica in humans it is possible to obtain from the stomach a small amount of secretion, possessing peptic power but no acidity. In some dogs the neutral chloride of the "sham-feeding" juice may be slightly higher than that of the "histamine" juice (*e.g.* 52 and 32 mg. per cent respectively—Toby, 1936); at all events, in both these types of gastric juice it constitutes only a very small proportion of the total chloride secreted.

What is the composition of pure, human gastric juice? The nearest approach to normal gastric secretion is that obtained in response to histamine administration. This secretion is uncontaminated, and neither diluted nor partly neutralized by saliva and the food substances of a test-meal. But, as we shall see later on, it merely represents the result of the secretory activity of one particular group of glandular cells, namely, the parietal cells. Miss Toby (1937b), working in our laboratory and in co-operation with the Royal Victoria Hospital, Montreal, analyzed the "histamine" gastric juice of some normal persons and some patients. Only absolutely pure samples of the juice were employed. Human "histamine" gastric juice was found to differ from normal canine gastric juice in the following respects. There was no great difference in the two juices as regards acidity and total chloride concentration, although the values for both moieties—especially for the acidity—were lower in the human gastric juice. The most striking difference was in the content of neutral chloride. Whereas in dog's histamine juice it averaged only 32 to 41 mg. per cent, *i.e.* 5.6 to 7.2 per cent of the total chloride, in normal human gastric juice secreted in response to histamine it averaged from 103 to 132 mg. per cent, *i.e.* 19 to 26 per cent of the total chloride. The concentration of the organic constituents (total nitrogen, dissolved mucin and pepsin) was also much higher in the human gastric juice. The concentration of pepsin was particularly high; very often it was as much as 2,000 Mett units, equalling the highest values for pepsin found in canine juice elicited by stimulation of the vagi. We cannot yet adequately explain such an abundance of pepsin in the human gastric juice. At all events Miss

Toby's observations show what a powerful and at the same time potentially dangerous digestive agent man possesses in the gastric juice.

(3) It has been conclusively established in our laboratory (Babkin, 1930; Vineberg and Babkin, 1931; Webster, 1931; Bowie and Vineberg, 1935; Toby, 1936), and independently of us by Gilman and Cowgill (1931), that the parietal cells are practically the only cells of the gastric glands that are stimulated by histamine, this substance exerting hardly any excitatory effect on the peptic and mucoid cells. It is true that under a small dose of histamine (*e.g.* 0.5 mg. to a dog of 15 to 20 Kg. body-weight) the concentration of pepsin and other organic substances in the gastric juice does not fall to an extremely low level or become practically nil, but it is incomparably less than in the juice obtained by means of sham-feeding (Webster, 1931). In a very carefully controlled investigation on man Welin and Frisk (1936), using a double gastric and duodenal tube, compared gastric secretions obtained with insulin (20 units) and histamine (1 mg.) respectively. Whereas the concentration of total chloride in the "insulin" gastric juice (15 m.eq. per liter) was only a little less than in the "histamine" gastric juice, the total acidity in the former (100 m.eq.) was markedly less than in the latter (150 m.eq.). On the other hand, there was a fair amount of mucus in the juice throughout the insulin test and only traces of it after histamine. This is proof that in man also histamine acts selectively on the cells of the gastric glands. No pepsin determinations were made by Welin and Frisk. Thus, even if it be maintained that histamine is capable of stimulating the peptic cells, it must be recognized that its effect is very weak and variable. In fact, it has been demonstrated in our laboratory (Alley, 1935) that histamine inhibits the secretory activity of the peptic cells and possibly that of the mucoid cells (chief cells of the neck).

Having regard to what has been said above (§2), and as might be expected, histamine produces a copious flow of gastric juice having a maximal content of total chloride and acid and very low peptic power. The first samples of juice obtained after histamine administration usually possess a moderate digestive power (for coagulated egg-white), which, however, quickly diminishes and may disappear altogether in the subsequent samples. This was attributed to the "washing-out" effect resulting when a flow of parietal secretion carries off the colloidal secretion of the peptic cells accumulated in the glandular tubules during a period of rest or of diminished activity of the gastric glands. The inhibitory effect of histamine on the secretory activity of the peptic cells must also be taken into consideration.

The above-mentioned peculiar action of histamine on the gastric glands is daily observed in the laboratory in experiments on dogs and cats. However, many clinicians do not agree that histamine exerts a similar effect on man, believing that the administration of histamine in the human subject results not only in a flow of acid gastric juice but also in an increased output of pepsin (Pollard, 1932; Bloomfield and Pollard, 1933; Rivers *et al.* 1936; Osterberg *et al.* 1936—to quote only the more recent papers). Miss Toby (1937a) in our laboratory re-investigated this problem on some patients in the Royal Victoria Hospital. First of all it must be remembered that usually a much

larger dose of histamine is injected in animals than in human subjects. Whereas the former receive from 0.5 to 0.66 and even 0.75 mg. per 10 Kg. of body-weight, the latter are given as a rule not more than 0.1 mg. per 10 Kg. Therefore Miss Toby proceeded to test in one and the same patient the effects of a small dose of histamine (0.5 mg.) and of a larger dose (1.0 mg.). With the smaller dose, the result was indefinite as regards pepsin concentration, but with the larger dose it was quite striking. As soon as the volume of the secretion increased, the concentration of pepsin fell, and it remained at the same low level or even fell still further when the flow of juice diminished. This is to be explained by the fact that, after most of the pepsin previously accumulated had been "washed out" from the glandular tubules, there was not a sufficient secretion of pepsin to restore the concentration of this enzyme in the juice to its former level.

Another special feature observed by Miss Toby in all the patients investigated was the so-called "fasting secretion" of the gastric glands. When the secretion provoked by histamine was superimposed on this continuous "fasting secretion," the very variable enzymatic content of the latter was reflected in the composition of the gastric juice. Therefore in man the output of pepsin cannot be taken as a true indication of the effect of histamine on the peptic cells, even though this substance may be credited with exerting some stimulatory effect. In their last paper Rivers and Vanzant (1937) recognize the phenomenon of the "washing out" of pre-formed pepsin during secretion provoked by histamine. However, they still maintain that histamine actually elicits a secretion of pepsin (unfortunately through some error they ascribe this function to the parietal cells). They employed a double histamine test in human subjects, administering small doses of the drug. The second injection of histamine, given ten minutes after the gastric secretion provoked by the first dose had greatly diminished, produced a less marked, though still considerable rise in the concentration of pepsin in the juice. These authors argue that, in the short interval between the two injections of histamine, pepsin could not accumulate in sufficient quantity in the tubules. Nevertheless, there is the possibility that this was so. In their experiments the maximum secretion of pepsin occurred during the twenty minutes following the first histamine injection and probably coincided with the initial copious secretion of fluid. Most of the parietal cells are located in the neck of the glandular tubules and only a few are found in their lower part, which is occupied chiefly by the peptic cells. Therefore pepsin has time to accumulate in this part of the tubules during the period when the parietal cells are less active, which lasted in Rivers and Vanzant's experiments from 30 to 40 minutes. The second injection of histamine produced at the beginning of the secretory period a maximal effect (for the dose of histamine employed) on all the parietal cells, including those situated at the bottom of the gland. It is probably the profuse secretion from these cells that washes out pepsin accumulated in the lower part of the tubules.

Another argument against Rivers and Vanzant's explanation is the fact that both the concentration and the output of pepsin continuously fell almost to the very end of the experiment. Even if it is the case that histamine is able to stimulate the activity of the peptic

cells, its positive effect must be neutralized in some degree by the inhibitory effect of the drug on these cells—a fact which Rivers and Vanzant have not taken into consideration.

I realize that at the present stage of clinical research on these problems and in their application to medical practice these details of glandular activity may seem unnecessary to the physician. But of what value then is the determination of pepsin in the gastric juice if the drug employed for the production of the secretion is a specific stimulant for only one group of cells, i.e. those secreting hydrochloric acid solution, and has no definite relation to the activity of the peptic cells and may even inhibit their effect? I repeat here what I said in 1930, namely, that histamine is the best known test for the functioning of the parietal cells and may be used with great advantage for the purpose of determining the ability of the human gastric glands to secrete fluid and hydrochloric acid, but nothing else.

(4) Such is the state of affairs in perfectly normal animals and in healthy humans. Under pathological conditions the relations are much more complicated. It is a fact of common knowledge among clinicians that in certain pathological cases the acidity of the gastric juice may be considerably below normal, whereas the concentration of total chloride may remain approximately at a normal level (Katsch, 1926, p. 450). Might these changes in the composition of the gastric juice be due to an excessive secretion of alkaline gastric mucus? Opinions on this point differ. A well known German gastro-enterologist, Katsch (1926, pp. 446 and 450), states definitely that cases of true "*Hypochlorhydric*" sometimes occur. By "*Hypochlorhydric*" he means a pathological condition in which some secretion is still produced, but the HCl concentration is greatly diminished or this constituent may even be completely absent from the juice. Under these circumstances the gastric glands lose their ability to concentrate acid up to the normal level, although the secretion of total chloride is little affected. Katsch proposes to discriminate between cases of achylia gastrica with cases and, without "*Hypochloric*." In the latter not only is the acidity of the juice diminished but the total chloride concentration as well. Later on the gastric glands may also begin to lose the capacity to produce gastric juice with a normal content of chloride, and the volume of the secretion may also diminish. Of the American clinicians, Chron and Reiss (1921) have drawn attention to a special type of gastric hypersecretion which is not accompanied by hyperacidity and may even be found in cases of complete anacidity.

On the other hand Welin and Frisk (1936) hold the view that there is no alteration in the mode of hydrochloric acid secretion in cases of hypoacidity. The submaximal values for the acidity they attribute to the decreased rate of gastric secretion and the neutralizing and diluting effect of the mucus being continuously produced by the gastric mucosa.

The clinical literature on gastric secretion is enormous and very conflicting. The chief criticism that may be made against the results of so many of the earlier investigations on man is the unsatisfactory technique employed in obtaining pure gastric juice. It was not until the introduction of the histamine, and later of the insulin test that the clinician had the

opportunity of studying a more or less pure secretion, although in the case of histamine not all the different cells of the gastric glands are activated but only those responsible for the formation of hydrochloric acid. As an investigation of pathological cases seemed to be so essential to an understanding of the normal secretory processes of the stomach, Miss Toby (1937a) at my suggestion studied the composition of the histamine gastric juice of some patients with gastric or duodenal ulcers, applying the same chemical methods as she used in the investigation of canine gastric juice. In this study only samples of juice that were absolutely uncontaminated with food-residues, saliva or duodenal juices were subjected to chemical analysis. It was found that in the gastric ulcer patients the acidity of the juice and its concentration of total chloride were lower, while the neutral chloride was much higher than normal. Whereas in normal persons the chloride present as neutral chloride constitutes from 19 to 26 per cent of the total chloride of the juice, in this group of patients it averaged 50 per cent of the total chloride. The volume of juice secreted in response to the same dose of histamine was on the average less than in normal persons. In the duodenal ulcer patients the acidity of the gastric juice and its concentration of total chloride deviated very little from the normal. The percentage of chloride present as neutral chloride was from 17 to 31, i.e. it was practically the same as in the juice of normal subjects. There was a tendency to hypersecretion.

How are these facts concerning gastric ulcer to be interpreted? One explanation might be that the ability of the parietal cells (1) to convert neutral chloride into hydrochloric acid, and (2) to concentrate chloride up to the normal level, becomes impaired. This is indicated by the lower concentration of the total chloride, the lower acidity and the abnormally high concentration of neutral chloride in the juice.

Another interpretation that suggests itself is that the secretion of gastric juice (of constant acidity) is diminished and therefore the acid is more effectively neutralized and diluted by the gastric mucus than normally. Unfortunately this simple explanation is unacceptable owing to the following facts. In some of the gastric ulcer cases the concentration of total chloride in the juice was fairly high (up to 480-490 mg. per cent) and the total acidity rather low (219-257 mg. per cent), although the volume of mucus was less than in normal subjects. In some other cases, where the rate of secretion was almost normal, the total chloride concentration (e.g. 320 mg. per cent) and the total acidity (e.g. 141 mg. per cent) were too low to be explained by a slight increase in the total secretion of mucus.

Yet another explanation of the peculiarities of the gastric juice in gastric ulcer patients might be offered, viz. that under pathological conditions the secretory activity of the various cellular groups lining the gastric tubules is altered quantitatively. The parietal cells then produce a less amount of acid secretion, as shown by the diminished volume of the gastric juice. On the other hand, the secretion of other cell groups—namely, the peptic cells, chief cells of the neck and surface epithelium mucous cells—may be increased. Therefore the secretion of neutral or slightly alkaline

fluid with a low concentration of chloride will be more abundant than under normal conditions. As a result, the gastric juice will be less acid, although the parietal cells will continue to secrete a fluid of constant acidity, and it will contain less total chloride and more neutral chloride. It is difficult to say which of these cellular groups is in a state of hypersecretory activity in a patient with gastric ulcer. The quantity of visible mucus produced by the surface epithelium varied greatly from patient to patient and in several cases was even lower than normal. Therefore this mucus can hardly be held responsible for the changes in the composition of the gastric juice of the gastric ulcer patients investigated by Miss Toby. Neither did the peptic cells display exaggerated activity in gastric ulcer patients, for the peptic power of the juice was *not at all high*. This was only to be expected, since the secretion of gastric juice was provoked by histamine. Furthermore, the peptic power varied greatly from case to case. It had no relation to the concentration of neutral chloride. Thus the "chief cells of the neck" remain the only group of secretory elements which may be held responsible for the dilution and neutralization of the acid parietal secretion. Unfortunately we have no direct proof that such is the state of affairs, but if this supposition is really correct then it is clear (1) that the chief (or mucous) cells of the neck are somehow affected by the ulceration process, and (2) that they respond to histamine stimulation to a far greater extent than under normal conditions.

I must frankly admit that none of these explanations satisfactorily answers the question under discussion. Whereas normally the activity of the different cellular groups in the gastric glands is strictly confined to one definite function or another and the activity of each group is finely adjusted to that of the others, in the diseased gastric mucosa these relations may be distorted. Under normal conditions the parietal cells produce a fluid secretion of practically constant acidity, and the peptic cells and mucous cells of the neck discharge their secretion with a minimal amount of fluid. In pathological cases several possibilities of deviation from the normal functioning may be assumed. Thus the activity of one group of cells may be increased over that of another; or a particular group of cells may lose its capacity to function with the same precision as normally; or another group of cells becomes overexcitable and now responds with exaggerated secretion to stimuli which under normal conditions hardly affect it at all. The physiologist seldom has the opportunity of observing these and other deviations from the normal. They may be studied perhaps by means of specially planned experiments in which the function of different groups of gastric cells is revealed. However this may be, before we accept any theory of gastric secretion which can be applied equally satisfactorily to the interpretation of normally and pathologically functioning gastric mucosa, a great many more experimental pathological, as well as carefully controlled clinical studies must be performed. I firmly believe that a full understanding of the secretory mechanism of the gastric glands can be finally achieved only through the closest co-operation between laboratory and clinic.

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Report of an Apparent Case of Secondary Pellagra*

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IT is rather surprising that after a considerable search no clear nor accurate description could be found dealing with the state of the rectum and colon during or after an attack of Pellagra.

Diarrhea is a common symptom in Pellagra and being common has apparently been accepted as diarrhea without further investigation. We find no detailed records of proctoscopic examination with descriptions as to what the mucosa may look like nor as to the structural state of the rectum and lower colon.

It would at least be interesting to know the results obtained from a series of post mortem studies upon the changes that take place in Pellagra. There may be such a study but the common disposition in the current literature is to speak of a diarrhea that has symptoms of variable degrees, sometimes preceding the other symptoms, and at other times present in severe form towards the end of the disease. That diarrhea occurs in Pellagra is evident, but it is not so clear just what destructive processes accompany this disease.

It has been shown that Pellagra occurs with, or secondary to, various chronic lesions of the intestinal canal, particularly those lesions that are destructive to the mucosa or those that interfere with the functions of this membrane.

Ian Murray (1), writing in the Glasgow Medical Journal, quotes Fakhry as finding that "a definite relationship between the incidence of Pellagra and intestinal schistosomiasis, and also recalled the fact that among sixty-five German prisoners of war who developed Pellagra, sixty-three were suffering from amoebic dysentery or bacillary dysentery.

Turner (2), in the American Journal of Tropical Medicine, makes the observation that "most of the exhaustive monographs in Pellagra give little information concerning organic lesion of the gastro-intestinal tract in this disorder. Most of them refer to chronic gastritis and ulcers in the large and small intestines." His work in the Charity Hospital has led him to the conclusion that gross organic disease of the gastro-intestinal tract may be associated with Pellagra much

more commonly than is generally detected. He reports 16 cases out of 75 seen as having definite gastro-enterological changes, most of which occurred in the lower or terminal gut.

Larimore (3) discusses a case in which for ten years there was persistent ill health marked by duodenal ulcers for which a number of operations were performed, including gastro-enterostomy, two explorations for hepatic abscess and re-operation for gastric and duodenal drainage. In this patient Pellagra developed.

Eusterman and O'Leary (4) discuss the probable secondary invasion by Pellagra and report 13 additional cases.

Numerous reports through the literature have led to the conclusion that Pellagra apparently does appear as a secondary manifestation in a proportion of individuals ill from various diseases of the gastro-intestinal tract.

The following report is that of a young colored male whose predominating symptoms were rectal and lower colon inflammation, that this inflammation was present for a long time preceding the pellagric symptoms, and that extensive changes took place in the rectum and sigmoid with marked deformity occurring.

HISTORY

A patient, J. J., Negro, male, age 23, admitted to the Atlantic City Hospital, April 23, 1935, with the chief complaint of diarrhea and pain in the rectum. The family history and past personal history were essentially negative. The history of the present illness revealed that a bloody diarrhea occurred about three years prior to the present time, at which time he had eight to nine bowel movements a day, lasting about four days; treatment not ascertained. Two years later, December 1, 1934, or five months prior to admission to the Hospital, there re-occurred the loose bowel movements having from nine to twelve a day with bleeding and griping pains in the abdomen, which condition persisted for approximately two months; during which time he had lost thirty-five to forty pounds. There was no loss of appetite at any time. For the next three months, the patient had only about five to six pass-

*From the Proctologic Service, Atlantic City Hospital.

ages per day. During these five months there was a progressive weakness and an occasional numbness of extremities.

PHYSICAL EXAMINATION

Revealed a very emaciated, young adult Negro male, with general physical findings essentially negative. The recto-sigmoidal examination revealed a marked wasting of the ischio-rectal space, external skin tags present, slight eversion of the mucous membrane and a complete loss of external sphincteric tone. A digital examination further disclosed no pathology. Upon passage of the sigmoidoscope evident ulcerations were noted beginning at the ano-rectal junction and extending well into the rectosigmoidal region. The ulcerations were deep, bled easily and profusely and were of no particular type or size with irregular spacing. There were areas of more or less normal mucous membrane between areas of ulceration.

Initial laboratory findings revealed a definite anemia, approximately three million R.B.C. with a 40% Hemoglobin, White Count showed no leucocytosis with a slightly abnormal increase of lymphocytes. Only slight kidney pathology was noted in the urinary examination. The blood Wassermann and Kline were both negative. The Frei test was negative.

Study from every standpoint was made from time of admission. However, the diagnosis of Pellagra was not arrived at until after a month, when the dermatologic manifestations made it evident.

Subsequent proctologic examination revealed a fairly rapid rectal involvement which was at all times the predominating feature of the case with the bowel movements ranging from four to seventeen per day. The ulcerations became more numerous and more closely set until a gradual coalescence occurred bringing about a gradual destruction of the bowel structure. Beginning about the eighth month there was notice of some stenosis with the formation of small adenomata which were rather numerous. Finally during the last month of life, the bowel became contracted into a small tubular canal; beginning about one inch above the ano-rectal line, it was hard, firm and more or less rigid, so that the proctoscope could not be passed. The area that could be seen was one mass of ulcerations without any areas of normal mucous membrane. When near the last a definite obstructive element came into play, an ileostomy was resorted to; finding in this

region at operation a bowel relatively free of involvement, which bore out X-ray findings, pre-operatively. This operation was resorted to mainly in an attempt to give the patient comfort. However, death occurred five days later.

Throughout hospitalization, during a twelve month period, numerous smears were taken directly from ulceration and many more stool examinations were made in an attempt to isolate Amoeba, B. Shiga, and B. Flexnor, diplostreptococci and other organisms with repeated negative findings; there being reported only those organisms normally inhabiting the gastro-intestinal tract. There was used empirically specific treatment for Amoebiasis. Bargain's vaccine was used as was all means of dietetic regimes and vitamin therapy, to no avail. The greatest amount of improvement, and that very slight, was believed discerned with the use of Calcium therapy with parathyroid extract. The blood picture was essentially unaltered by numerous transfusions and various other means. The range in weight was from ninety to one hundred pounds.

In this individual the predominating symptoms were those of an intense colitis and these symptoms were justified when examination by proctoscope was made.

The gross change in the bowel was perfectly obvious as well as extensive, producing in the ampulla of the rectum such changes in shape, size, and contours, that the finger could not be passed and eventually produced obstruction.

This violent inflammation had been going on for months before there was any change in mental state, nervous phenomena or skin manifestations. These changes in mental state, and dermatologic findings came so late in the disease that we were led to believe that the Pellagria state could have been secondary to the ulcerative colitis.

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A Case of Peptic Ulcer in a Child Following Brain Injury

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A POSSIBLE relation between intracranial lesions and the presence of gastro-intestinal ulceration had been suggested repeatedly but not until 1932, when Cushing published his review of this subject, was this a commonly recognized and accepted observation.

Cushing reported three cases of acute perforating

gastro-intestinal lesions which followed operations for cerebellar tumor. He also cited two cases of gastric erosions following operations for brain tumor, two cases of gastric ulcer associated with malignant hypertension with choked discs, the case of a child of ten with a chronic cicatrizing duodenal ulcer associated with a recurring cerebellar tumor, and the case of a

man with duodenal ulcer who had recurrence of gastric distress associated with each of three exacerbations of intracranial symptoms from a radio-sensitive tumor encroaching on the third ventricle.

In verification of his observations the experimental production of gastric and duodenal lesions following various intracranial procedures has since been accomplished by Keller and his associates, who found that lesions in the neighborhood of the third ventricle were prone to produce changes in the gastro-intestinal mucosa, either hyperemia, erosion, or crater formation.

Although these observations are significant because of their bearing on theories of the etiology of ulcer their importance is lessened because of the rareness of reported cases in which there is an unmistakable connection between the intracranial and the gastro-intestinal lesions. The actual incidence of such cases may be greater, however, than appear at this time. For this reason the following case is worthy of being placed on record:

The patient was a boy of eleven years, somewhat below average stature, but well nourished, vigorous and healthy. According to his mother's story, the only illness he had ever had occurred at long intervals, and consisted of "biliary spells" by which she meant spells of nausea, vomiting and constipation, accompanied by slight fever. After a dose of castor oil he always recovered promptly.

On October 22, 1936, he was struck by a truck and knocked unconscious. He regained consciousness after a few minutes and was later taken to the hospital where he was treated for concussion and an injured right foot. During the first twenty-four hours after the injury, he vomited repeatedly, but improved rapidly thereafter, and was allowed to go home on the fourth day and to return to school in another ten days.

Twenty days after the accident he began to complain of a dull aching in his frontal region particularly above the left eye, occurring usually in the morning hours shortly after arising. There was some vertigo and occasional diplopia. His eyes burned and hurt him if he read. His appetite began to fail at this time and he complained of sharp, severe pains in the epigastrium a little to the left of the mid-line. The pains occasionally occurred as he was eating, lasted for a few minutes and then subsided.

Six weeks after the injury he was first seen by Dr. Brown, who made a diagnosis of contusion and laceration of the brain with sequelae of headache and disturbance of vision. The extent and location of the brain lesion could not be determined in the absence of localizing signs. He was extremely nervous. Lumbar puncture showed an increased cerebro-spinal fluid pressure of 180 m. m. of water. The treatment prescribed consisted of a low fluid—low salt diet, rest, and one and one-half grains phenobarbital daily.

Dr. T. J. Vanzant investigated the visual disturbance and found a marked convergence insufficiency with a near point of convergence at 600 m. m. Orthoptic training was instituted.

Because the differential blood count revealed a ten per cent eosinophilia, examination of the stools were made with the result that it was discovered that they contained a large amount of blood. The boy had not noted that his stools were tarry but the mother recalled that on December 18 and again two days later the boy had suddenly grown quite pale and felt weak.

Fluoroscopic examination of the stomach and duodenum was then requested and showed a normal stomach, but the duodenum was small, irritable, and showed a constant deformity. A diagnosis of superficial duodenal ulcer was made.

He was then placed on a diet consisting of six feedings of bland food, restricted as to liquid and to salt content. He was given six doses of an aluminum silicate preparation each day. The dosage of phenobarbital was increased to two and one-fourth grains daily. On this management headache disappeared, nervousness was controlled, and abdominal pain ceased. There was no recurrence of gross bleeding, and repeated stool examinations disclosed no occult blood.

After one month the diet was made more liberal but the salt and water content was kept low and coarse foods were prohibited for two months more at which time he had apparently recovered from all evidence of intracranial and gastro-intestinal disturbances. The eye condition returned to normal under orthoptic training, the near point of convergence decreasing from 600 m. m. to 40 m. m.

Since the history prior to the accident had never suggested the presence of a duodenal ulcer, which is, of course, extremely rarely diagnosed in children of this age, and since the ulcer seemed to be an acute, shallow, recent one from the X-ray appearance, we conclude that it arose during convalescence from the brain trauma. It is to be recalled that there was recurring vomiting for the first twenty-four hours after injury, after which his condition rapidly improved. It was not until post-concussion symptoms appeared that epigastric pain and melena occurred.

Since the patient was suing for compensation the question of prognosis was important. Would the well known tendency for ulcer to recur be manifest in this boy later in life? If the injury to the brain was the precipitating factor in the development of the ulcer, we would not expect recurrence of trouble in the duodenum unless there should be recurrence of neurological symptoms also.

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Unusual Hematemesis or Gastrorrhagia

Hereditary Hemorrhagic Telangiectatic Dysplasia with Gastrostaxis or Stomachorrhagia (Goldstein's Hematemesis)

By

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GASTRIC hemorrhage is frequently looked upon as a catastrophic and serious complication. Rarely one meets with massive hematemesis that does not require emergency or operative interference. The occurrence recently of two cases with recurrent massive gastrorrhagia due to gastric telangiectatic dysplasia in the same family lead me to make these few remarks.

In such cases, injections of Moccasin snake venom (Lederle's, N. Y.), as used by Peck & Rosenthal, of Mt. Sinai Hospital (New York)—[Arch. Dermat. and Syphil., 35:831-864, May, 1937] may be effective in checking and preventing such telangiectatic bleeding. Russell viper venom ('Stypven,' B. & W., London), in solution, given orally, has checked gastric bleeding.

In addition to these measures, one may use (intravenously) Congo red solution and calcium gluconate, with or without intramuscular injections of parathormone, where blood transfusions are not possible or have failed to control the bleeding. Concentrated liver extract injections and cebione or (ascorbic acid and vitamin "P") may also be helpful.

Gastric bleeding, when not due to ulceration, neoplasm, polyposis, portal thrombosis, gastric allergy, hepatic cirrhosis, varices, blood dyscrasias, Geisböck's disease, "haematemesis puellaris," arterial nevus or varix of the lower end of the esophagus, angioneurotic edema, thrombophlebitic spleen, erythema multiforme with gastro-intestinal manifestations (Osler), splenic anemia (Banti's disease or "Klemperer's anemia"), other severe anemias, leukemias, Hodgkin's disease, scurvy, gastritis, and uremic states, may sometimes be explained by the presence (noted gastroscopically) of gastric telangiectases in patients suffering from *Rendu-Osler-Weber's disease* or *Goldstein's Hereditary familial Angiomatosis* with recurring hemorrhages.

Of interest in this connection are the reports by John Abercrombie (1780-1844)—[IV. "Haemetemesis" in "Pathological and Practical Researches on Diseases of the Stomach, The Intestinal Canal, The Liver, and Other Viscera of the Abdomen"—pp. 80-81, 1828, (London and Glasgow), Edinburgh, Waugh and Innes]; Sir George Burrows ["Constitutional hæmatemesis, particularly in females"! Tweedie's Library of Medicine, Vol. 5, p. 38, 1840]; T. H. Sawtell [Clinical Society's Transactions, London, 19:1-4, 1886]; W. Hale White ["Gastrostaxis" or "Hæmatemesis without ulceration," Lancet, Vol. I, No. 4061, 1819-1820 (June 29), 1901; No. 4340, II, 1189-1195 (Nov. 3), 1906; Vol. I, p. 416, 1912]; Donald W. C. Hood ["Hæmatemesis, with special reference to that form met with in early adult female life"—Trans. Med. Society of London, 15:283-297, 1892]; James Hamilton ["Observations on the Utility and Administration of Purgative Medicine in Several Diseases"

—6th Chapter: pp. 108-117, 1805, Edinburgh, C. Stewart]—speaks of "one variety of hæmatemesis which attacks females who are from eighteen to thirty years of age; and it rarely appears sooner"—(Vicarious menstruation), and J. Lordat (1773-1870) of Montpellier—[Traite Des Hemorrhagies, p. 6 and p. 86, 1808, Goujon, Brunot-Labbe, Paris; "First Lines of the Practice of Physic," Book IV, Chap. I, Sec. II, Para. 744, etc.—In Chapitre IV, ("Hemorrhagies par fluxion locale"; 3e Genre.), p. 86, Lordat refers to the report by Helwich (Morb. Uratislav., 1701)].

Ashwell ["Chlorosis and its Complications"—Guy's Hosp. Reports, Vol. I, 1836] regarded chlorosis as connected with amenorrhea and stated "a vicarious discharge of blood from the stomach by vomiting is not an unusual concomitant of protracted chlorosis and amenorrhoea." W. Leube alludes, also, to such possible association [Ziemssen's Cyclopaedia of the Practice of Medicine, Vol. VII, 271 and 274, English Transl., 1876, Wm. Wood & Co., New York; "Hemorrhage of the Stomach," pp. 269-293].

Sir George Burrows (1840) speaks of hematemesis independent of any apparent change of structure in the mucous membrane of the stomach or in any organ capable of influencing the circulation through that membrane "is certainly rare," although he believes he has met with several such cases. "Such cases usually occur in women between 30 and 40 years of age."

Reference should here be made to the publications by Dalche ["Essai sur L'Émbaras Gastrique Et Le Vomissement De Sang"—An. XI, 1803, Paris Thèses—Vide pp. 29-66—"Hématemese Ou vomissement de Sang"] who gives a historical review referring to early observations by C. Pinel, Henricus ab Heer, Riverius, Hippocrates, Hoffmann, Joh. Rhodius, Bartholinus, Lieutaud, de Lorry, Juncker, C. Portal, Morgagni, etc.; Latour (1828); W. P. Herringham [St. Bartholomew's Hosp. Reports, XLIV, 11-21, 1909]; A. G. Gullen (1906); B. Dawson (1905); Osler (1902), and Helwich (1701).

Helwich spoke of a woman who was 40 years old and had borne several children. Every year, in the Spring, at the end of the Summer, and in the Autumn, she brought up a quantity of blood from the stomach for a period of four days.

D. Latour (1828) says that Portal, Franck, Hoffmann, VanSwieten, Baldinger, Warton, and others have observed that among those who have died from gastro-intestinal hemorrhage, the mucous membrane of the stomach and intestine may not show any lesion from which the blood came! [Histoire Philosophique et Médicale des Hémorrhagies, Vol. I, 287, 1828, Paris].

Dalche (1803) says that gastric bleeding without lesions are commoner in virgins and that the hemor-

rhage most usually occurs in the Spring and Autumn, and mentions further, that after death there may be no erosion of the internal surface of the stomach.

Ashwell ["Observations and its Complications"—with cases—Guy's Hosp. Reports, Vol. I, 529-579, 1836] reports Cases 5, 6, 7, 8 and 9, which are of particular interest in connection with the above remarks. In Case 5, he reports a delicate girl of 16 years, suffering from "chlorosis complicated with vicarious discharge of blood and disorder of the stomach and bowels"—(pp. 561-562). She had severe attacks of hematemesis and occasional epistaxis, and two lighter attacks of gastric hemorrhage.

Richard M. Smith and Sidney Farber, of Boston, discuss splenomegaly in children with early hematemesis (Jour. of Pediatrics, 7, No. 5, 585-608, Nov., 1935).

Bertrand Dawson [Brit. M. J. II:1032, 1905] believes hematemesis in young women to be due to the menstrual molimen, if not to vicarious menstruation, and used the term "*hæmorrhagic gastralgia*," while Donald W. C. Hood's term (1892) is "*hæmatemesis puerilis*."

The case of fatal hematemesis, reported by Carnot, Rachet and Delafontaine [Bull. et mém. Soc. Méd. d. hôp. de Paris, 53:538-541 (May 13), 1929] was due to hemorrhage from an arterial nevus of the esophagus.

W. P. Herringham ["On Gastric Ulcer and Gastrostaxis." St. Bartholomew's Hosp. Reports, 44:11-21, 1909] commends (p. 12) on a form of hematemesis in young women akin to the epistaxis common among boys, and which might be called, by Hale White's term, "*Gastro-staxis*" (1906) or dripping of blood from the stomach. He showed a case of gastric bleeding not dependent upon ulcer.

Sir Thomas Watson, in his Lectures [Vol. II, p. 496, 1871, 5th Ed.] also mentions hematemesis occurring as vicarious menstruation.

W. Hale White collected 29 cases of gastrostaxis [Lancet, No. 4340, 1189-1195 (Nov. 3), 1906] and states "are not some patients said to be afflicted with gastric ulcer really suffering from a different disease?" He says further, frequently in women, between 20 and 40 years, associated with chlorosis, and at times occurring apart from chlorosis, hæmatemesis is met with, without any ulceration.

Gastric capillary hemorrhages are not uncommon as the result of increased permeability of the mucous membrane caused by allergic reactions. Sante (1936) reported massive hemorrhage from the gastro-intestinal tract attributed to allergy. Gastrorrhagia, due to allergic reactions, have also been reported by Andresen (1934); R. A. Gutmann (1932); Crispin (1915 and 1916); Morris (1904); Halstead (1905); Osler (1904 and 1914); A. Tzanck (1932); Dutton and Lintz (1925); Albert Rowe (1937), and others have mentioned gastro-intestinal bleeding due to food allergy.

We might recall Vidal's "*COLLOIDCLASSIC DIATHESIS*," and Bray's "*ALLERGIC DIATHESIS*" or the inheritance of the tendency to develop allergic reactions—the transmission of allergic propensities, (such as are rarely, if ever, observed in animals).

Rowe (1937) states: "an exaggerated tendency to allergy is not only transmitted, but that the tendency to develop certain types of allergy such as pollen, animal emanation, or food allergies often is inherited." [Rowe: Clinical Allergy, p. 45, 1937, Lea & Febiger, Philadelphia].

Gastro-intestinal allergy occurs not infrequently in patients suffering with bronchial asthma, especially when due to food sensitization.

Enfield [Amer. J. Digestive Dis. and Nutrition, 3, No. 1, 69-70, March, 1936] reported on "Gastro-Duodenal Hemorrhage of Unknown Origin."

Osler spoke of "Hereditary angioneurotic edema"—[Am. J. Med. Scs., 95:362, 1888] and discussed "The Visceral Lesions of Purpura and Allied Conditions" [Brit. Med. J., I:517, 1914]. An important contribution by Osler was his paper "On the Surgical Importance of the Visceral Crises on the Erythema Group of Skin Diseases"—[Am. J. Med. Scs., 127:751, 1904].

Mention of interesting instances of gastric bleeding, not due to any organic lesions in the stomach, was made by Stephen Mackenzie; Habershon; Sidney Phillips (1887); Jacques Lordat (1808); Andral (1828); Chomel, and Prof. W. Leube, of Jena.

Norah Schuster's (Jan., 1937) case of "*familial telangiectasia*" showed numerous gastric and duodenal telangiectases with multiple aneurysms of the splenic artery at necropsy [Jour. Path. and Bact., 44, No. 1, 29-39, Jan., 1937].

Probable cases of gastrostaxis and telangiectatic dysplasia of the stomach with gastrorrhagia (or "Goldstein's hematemesis") were those reported by Ullman, of Vienna (1896, 1900); W. H. White, of London (1906, 1912); Pons, Meine and Blunkle, of Asbury Park (1929); L. N. Boston, of Phila. [Am. J. M. Scs., 180:798, Dec., 1930]; White [The Lancet, I, No. 4061, 1819-1820, (June 29), 1901]; Guttmann, Laval and Schlumberger (1932); Benhamou (1933); Kessel [J. A. M. A., 97:1058 (Oct. 10), 1931]; H. I. Goldstein [Brit. Med. J., No. 3937, 1275 (June 20), 1936; Arch. Internal Med., 48, Part I, 836-865, Nov., 1931; Acta Dermato-Venerologica (Stockholm) XIII: Facs. 6, 661-694, Dec., 1932; Arch. Dermat. and Syphilol., 26:282-308, Aug., 1932]; "Goldstein's Hematemesis," J. A. M. A., 108, No. 14, 1202 (April 3), 1937]; Thomas FitzHugh, Jr., of Phila. [Am. J. M. Scs., 166:884, Dec., 1923; 181:261, Feb., 1931]; Matthew S. Ersner, of Phila., in his discussion of Goldstein's paper before the Medical Society of New Jersey, June 13, 1930, mentioned two cases of gastric bleeding of telangiectatic origin. The father of one of the patients mentioned by Ersner, suffered from stomachorrhagia, which led to an exploratory laparotomy, but apparently nothing was found at operation, and there was no abatement of the gastric bleeding! Other members of this man's family suffered from severe recurring attacks of nosebleed and numerous telangiectases ["Hereditary Epistaxis; with and without Hereditary (Familial) multiple Hemorrhagic Telangiectasia"—Jour. of the Med. Society of N. J., 28, No. 4, 309-327, April, 1931, Ersner's Discussion, pp. 326-327].

The Action of Histidine on the Gastro-Intestinal Tract*

By

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HISTIDINE has recently been proposed and used for the parenteral therapy of peptic ulcer. The experimental work of Weiss and Aron (17, 18, 19) in five Exalto-Mann-Williamson dogs (E.M.W. dogs; transplantation of pancreatic and biliary portion of the duodenum into the terminal ileum, with continuity of the gut restored by anastomosis of pylorus and jejunum) has formed the meager background for the clinical use of this amino acid. Histidine apparently prevented gastrojejunal ulcers regularly occurring in these preparations. It was suggested that the inability of these dogs adequately to digest proteins resulted in a deficiency of essential amino acids, and that one of these, histidine, was necessary for the maintenance of the integrity of the gastro-intestinal epithelium.

The small number of animals and brief period of observation used by the above authors, however, rendered their work open to criticism. The recent report of Fauley and Ivy (2) on a large series of E.M.W. dogs shows that ulcers can be prevented by a special diet or fundusectomy. The conclusion that gastric acidity is more important than nutrition in the etiology of these ulcers is also supported by the experiments of Morton (10) who showed that such ulcers in dogs with surgical duodenal drainage into the ileum will heal if the stomach is again anastomosed to the jejunum at a point distal to the original ulcer. Barry and Florey (1) using the Matthews and Dragstedt operation on cats and young pigs (small fundic pouch anastomosed to the terminal ileum) were unable to demonstrate any prophylactic effect of histidine on the resulting ulcers. Stalker, Bollman and Mann (14) have shown that histidine will not prevent the formation of cinchophen ulcers in dogs, and Windwer and Matzner (20) were unable to prevent ulcer formation in rats (pepsin-HCl method) by using histidine. Indeed, they found that normal rats developed ulcers if injected with the amino acid.

The only report that might be considered as partially confirmatory of the original work of Weiss and Aron is that of Flood and Mullins (3). Of twelve histidine treated E.M.W. dogs, 45 per cent were apparently protected from ulcer formation, whereas all five control dogs developed ulcers. Elaborate chemical and pathological examinations, however, failed to show any difference between the control and histidine dogs to which the results might be attributed. Very recently, Sandweiss, Salzstein and Glazer (11) reported that in fourteen histidine treated E.M.W. dogs, 13 or 93 per cent showed ulcer formation; twelve controls all developed ulcers. They suggested that the results of Flood and Mullins may be due to the fact that the

latter workers divided the duodenum slightly below the pylorus, and that the duodenal stump remaining attached to the stomach possibly prevented the occurrence of ulcers.

Early clinical reports on the therapeutic efficacy of histidine injections in peptic ulcer patients were uniformly enthusiastic; but a careful scrutiny of these publications reveals few control studies, a lack of rigid selection of patients and criteria of cure, and no analyses of late results. Volini and McLaughlin (15) claimed that histidine reduced both the volume and acidity of gastric secretion of patients in response to test meals and histamine, and Gardiner (5) apparently confirmed this finding. All other workers have been unable to substantiate these results. In a later report, Volini and McLaughlin (16) suggested that histidine may act by virtue of stimulating a histaminase, which, in turn, inactivates histamine; thereby gastrin (gastric "secretin") is inhibited, thus reducing gastric acidity, secretion, and motility.

More complete and critical studies on large and adequately controlled groups of peptic ulcer patients have recently appeared, especially those by Sandweiss (12, 13), Martin (9) and Flood and Mullins (4). The conclusions were reached that the effects of histidine injections are mainly symptomatic and transient; that the extravagant claims made for this amino acid are unwarranted; that although parenteral therapy may be of some value in the small percentage of cases failing to respond to diet-alkali management, saline or distilled water injections produce as prompt and dramatic relief as does histidine. The possibility looms large, therefore, that the therapeutic effect of histidine is a psychic one.

When the experiments to be communicated in this paper were first undertaken (September, 1935), it seemed desirable to test in the laboratory effects of histidine on gastric function. Many clinicians were using histidine in an uncritical manner, and controlled laboratory studies of the possible gastro-intestinal actions of histidine were quite meager. The purpose of the study was to determine if histidine injections in any way altered the secretory response of gastric pouch and gastrotomized dogs previously standardized either to a histamine stimulus or test meals. In addition, *in vitro* tests were made of histidine effects on the tone and motility of rabbit intestine.

METHODS AND PROCEDURE

Animal Experiments: Five healthy adult female dogs were used. Three gastric pouch animals were prepared in the usual manner; in two, the accessory stomachs were innervated, the third was an Heidenhain preparation. Erosion of tissue about the pouch openings was prevented by a simple self-retaining rubber catheter technic devised by the authors (6), and alkali dressings were in this way

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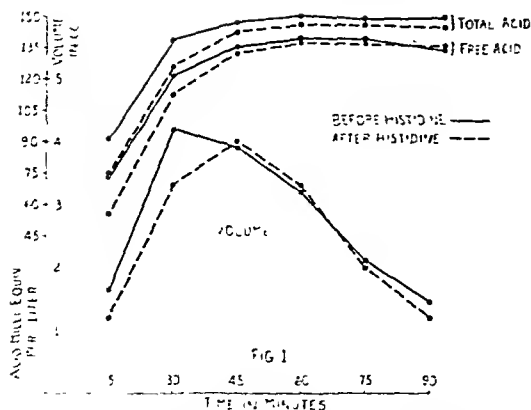


FIG. 1. Gastric secretory response to histamine before and after histidine. Pavlov gastric pouch dog E. Weight, 16 kg. Each curve constructed from average values of at least ten trials. There is no appreciable change in either volume or acid values following a course of histidine.

completely eliminated. Two dogs were gastrotomized, and similar catheters with removable glass stoppers to prevent spillage of gastric contents were kept permanently in place. The pouch dogs were trained to the usual harness collection apparatus, and the routine precautions regarding Pavlov gastric pouch animals were carefully observed.

Standardization and testing were done as follows: One Pavlov pouch dog (E) weighing 16 kg. was standardized during ten trials for its fasting gastric response to histamine base, 0.1 mgm. per kg., administered subcutaneously as the acid phosphate salt. Samples were taken at fifteen minute intervals until resting values returned. Histidine* was then given intramuscularly once daily for thirty injections in the dose of 0.2 gm. (5 c.c. of a 0.4% solution of the monohydrochloride). During and after the course of histidine, dog E was again tested at intervals with histamine. At the conclusion of the histidine injections the responses to test meals of 450 grams of lean hamburger were also determined in this animal, and compared with known preinjection values for such test meals.

The two other pouch dogs were standardized to test meals over a period of eight weeks. Dog T, weighing 15 kg., with an innervated accessory stomach, received 300 grams lean hamburger, and dog J, weighing 20 kg., and with extrinsic nerves to the pouch severed, received 450 grams of a commercial dog food, Red Heart A, consisting of cereal, beef, soy bean flour, yeast, and cod liver oil. Hourly collections of pouch secretion were made until fasting levels returned, the volumes recorded, and acid values titrated. After adequate standardization, daily intramuscular histidine injections were given in the dose and number stated above with the exception that dog T received additional injections twice daily for ten days following the routine thirty doses. Experimental runs were made thrice weekly during standardization, twice weekly during the course of histidine injections, and once or twice weekly thereafter for from five to ten months. Pouch dog T, because of a very large accessory stomach secreting as much as 150 c.c. per hour at the height of response to the test meal, required the daily oral administration of supplementary sodium chloride in capsules in order to maintain a normal electrolyte balance.

The two gastrotomized dogs, A weighing 14 kg., and R, weighing 12 kg., were standardized to test meals of 300 and 200 grams of lean hamburger respectively, over a

period of two months. Thirty daily injections of histidine in the dose stated were then given, during and after which the gastric responses to the test meals were examined twice weekly. Samplings of gastric contents were made through the catheter at intervals until the stomach was empty. The samples removed were approximately 4 c.c. in volume. Such collections were immediately heated to boiling to arrest peptic digestion, centrifuged, the per cent of solid content recorded, and the supernatant juice analyzed as described below.

All specimens of pouch juice or gastric contents were titrated in one c.c. portions against N/50 NaOH delivered from a microburette. Töpfer's and phenolphthalein indicators were used to determine the free and total acid values respectively. Results were recorded in milliequivalents of acid per liter of gastric secretion or contents.

Gastro-intestinal fluoroscopic examinations* were made in pouch dogs E and J to determine emptying time and motility. Direct examinations of the mucosa of the accessory stomachs were made periodically with the aid of a cystoscope passed through the pouch opening.

In Vitro Experiments: Isolated strips of rabbit ileum were studied in an organ bath to determine the effects of histidine on intestinal tone and motility. Dilutions ranging from 1:500 to 1:2,000,000 were tested. Oxygenated Ringer-Locke solution at 37.5° C. was used as the bath fluid, and graphic recording of the smooth muscle contractions was made by means of the usual muscle lever-kymographic apparatus.

RESULTS

All the dogs remained in good health and maintained or increased their weights during the period of observation. No untoward local or systemic reactions to the histidine injections were seen. Direct examination of the pouches revealed normal gastric mucosa in all instances throughout the experiments.

I. Secretory response to histamine.

In Fig. 1 are shown the acid and volume responses to histamine obtained in gastric pouch dog E. This animal had a small pouch which secreted an average of around 4 c.c. in the fifteen minute period of maxi-

*We are indebted to Dr. H. M. Wilson for these tests.

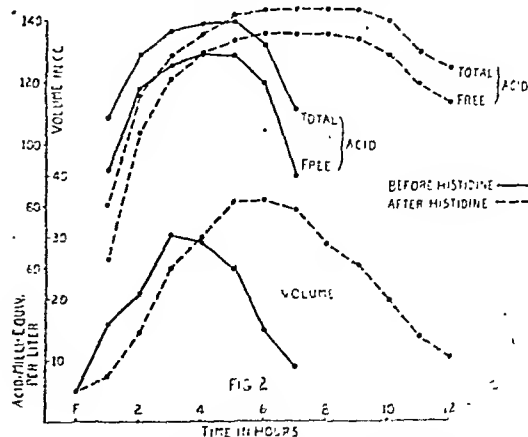


Fig. 2. Secretory response of accessory stomach to test meal before and after histidine. Heidenhain gastric pouch dog J. Weight, 20 kg. Fed 450 grams mixed meal. The pre-histidine curve represents the average of 25 experiments; the post-histidine curve, 45 trials over a period of ten months. Note the prolongation of the secretory period.

*The histidine used was Larostidin, kindly furnished by Hoffmann-LaRoche, Inc.

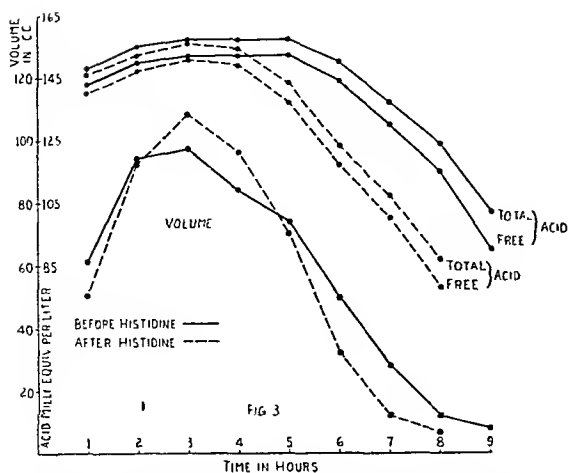


Fig. 3. Gastric secretory response to test meal before and after a course of histidine. Pavlov gastric pouch dog T. Weight, 15 kg. Fed 300 grams lean hamburger. Pre-histidine curve represents the average values for 20 standardization experiments; the post-histidine curve, the average of 18 trials. There is no significant alteration due to the injections.

mal response to histamine. Each value in the curves represents the average of at least ten determinations. It is at once evident that no appreciable difference occurred in either the volume or acidity of the pouch juice produced by histamine stimulation before, during or after the course of histidine.

II. Secretory response to food in gastric pouch dogs.

In none of the three dogs used in these experiments was there any evidence obtained that the gastric secretory response to food decreased either in volume or acidity after treatment with histidine. To the contrary, in two of the animals studied there occurred an increase in the secretory response to the test meal, due largely to a prolongation of the period during which secretion took place.

In Fig. 2 are presented the results obtained in Dog J which also typify those obtained in Dog E. The pre-histidine control curves for volume and acid response to the meat meal in this dog represent the averages for a two month standardization, and are characteristic of the normal type of secretion curves resulting from food in gastric pouch dogs. Secretion lasts approximately eight hours after feeding, with the peak response during the third to fifth hour. As one might predict, the acid values closely parallel the volume response. This type of food response in dogs is so constant that it may be considered a physiological norm. The pouch in this animal was a moderately large one and secreted around 35 c.c. of juice per hour at the peak response. After the administration of thirty injections of histidine, the period of pouch secretion was prolonged to twelve hours, with peak secretion now occurring between the fifth and seventh hour after feeding. Due to this prolonged secretion, the total volume of pouch juice secreted in response to the meal increased from a pre-histidine value of approximately 150 c.c. to 300 c.c. The acid values continued to follow the volume curve. These changes are clearly shown in Fig. 2. The alterations in the secretory curve were discernible as early as the second week after injections

were started, increased to reach a maximum about two weeks after histidine was stopped, and diminished gradually over the ten months during which observations were continued. The post-histidine secretion curve of pouch dog E was quite similar to that shown in Fig. 2 in respect to the prolongation of the secretory period and the resultant increase in the total volume response to the test meal. After histidine, peak response to feeding occurred nine to eleven hours after feeding and a fasting level was reached only at the fourteenth hour.

The fluoroscopic examinations undertaken in these two dogs, to ascertain whether delayed gastric emptying time was the basis for the protracted post-histidine secretory response to food, were made by mixing sufficient barium sulphate with the standard test meals and screening the animals at intervals. Gastric motility appeared to be within normal limits for dogs, and the stomachs of both the animals were completely empty roentgenologically six hours after feeding. This suggests that gastric secretion continued for about six hours after the stomach had emptied. The inferences drawn from these fluoroscopic studies, however, should be exceedingly guarded, as the procedure required a break in the usual experimental routine to which the dogs were trained. Furthermore, the dogs were fed barium with their test meal, and the emptying time of this type of meal may not be directly comparable to that of the test meal.

The third gastric pouch dog T, with a peak secretion following food reaching at times as high as 150 c.c. of pouch juice per hour, failed entirely to show any notable alteration in gastric secretory response after fifty injections of the amino acid. This dog differed from the other two preparations only in having a very large accessory stomach, and thus requiring supplementary sodium chloride to maintain its electrolyte balance. In Fig. 3 is shown the volume and acid response of this animal before and after histi-

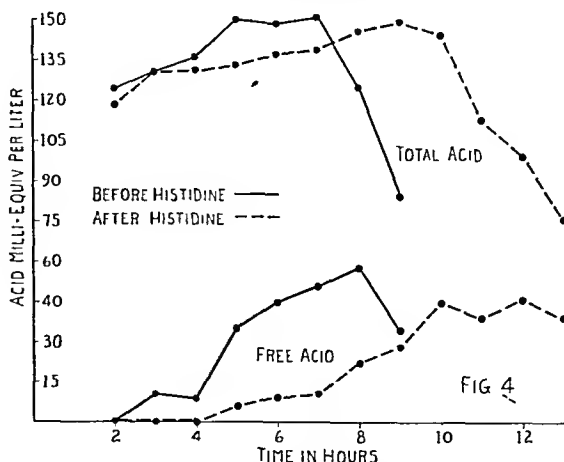


Fig. 4. Gastric secretory response to test meal before and after histidine. Gastrotomized dog A. Weight, 14 kg. Fed 300 grams lean hamburger. Total and free acid values of samplings, collected until stomach empty. Pre-histidine curve plotted from the average of 20 standardization experiments; post-histidine curve, 20 trials. Note delayed gastric emptying, and the lag in appearance time of appreciable amounts of free acid following the administration of histidine.

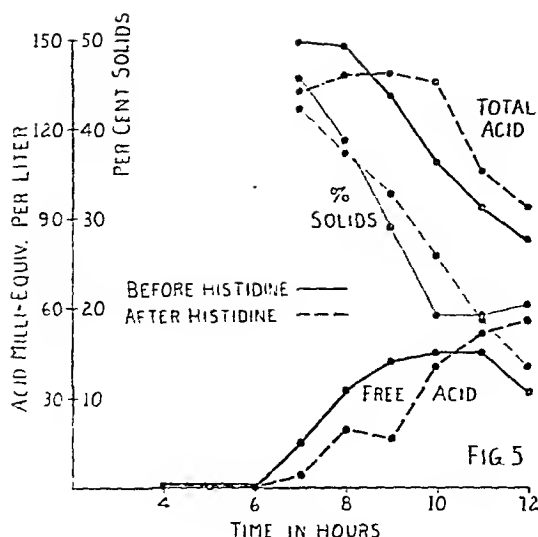


Fig. 5. Gastric secretory response to test meal before and after histidine. Gastrotomized dog R. Weight, 12 kg. Fed 200 grams lean ground meat. Total and free acid values and per cent solids of gastric samplings, collected until stomach empty. Pre-histidine curve constructed from the average of 25 experimental runs; post-histidine, 12 trials over a period of two months. There is no such delay in gastric emptying time as seen in dog A, Fig. 4.

dine administration, and it is clear that no significant change has occurred. Observations continued at intervals up to six months after injections were stopped did not differ from the values indicated in the post-histidine curves depicted in the figure.

III. Secretory response to food in gastrotomized dogs.

Two gastrotomized dogs were studied in order to obtain a more dynamic picture of any changes in the secretory response to food induced by histidine. This type of preparation enables one to obtain information about the gastric emptying time without the complicating factors of barium meals and fluoroscopy, or passage of stomach tubes. By ascertaining the amount of solid food remaining in the stomach at any given interval after feeding, information is gained concerning the motor as well as the secretory activity of the stomach.

Gastrotomized dog A showed changes after histidine similar to those observed in two pouch dogs. Fig. 4 represents the total and free acid values of the hourly samples taken during the response to the test meal before and after a course of histidine injections. It is apparent that the post-injection secretory response was prolonged four hours, and that there was a delay in the appearance of significant amounts of free acid. Inasmuch as the very late samples still contained some food, it would seem that a delay in gastric emptying time rather than a lag in secretory response accounts for both the prolonged secretion and the late appearance of free acid. These changes were fully evident a short time after completion of the injections, and persisted for the four months during which observations were continued.

Gastrotomized dog R, on the other hand, failed to show any alteration either in emptying time or acidity values after the amino acid. The results in this animal are shown in Fig. 5, which also includes an index of the per cent solids in the gastric samples. No prolongation of secretory period and no delay in the appearance of free HCl occurred.

IV. In vitro experiments.

Isolated strips of rabbit ileum were studied in an organ bath to determine the effects of histidine on the smooth muscle of the enteric tract. The intestinal strips were shown to be reactive not only by the character of the tone and peristalsis exhibited, but also by tests before and after the histidine experiments with acetyl-beta-methyl-choline (1:12,000,000 and 1:6,000,000) and with B-diethyl-aminoethyl-diphenyl acetate hydrochloride (1:2,000,000), which have parasympathetic spasmodic and antispasmodic actions respectively. The results of these tests revealed that histidine produced no discernible effects either on the amplitude or frequency of contractions, or the tonus of the intestinal segments in dilutions which can at all be considered within physiological limits (1:2,000,000 to 1:50,000). Nor did the amino acid have any influence in dilutions as low as 1:10,000. In dilutions of 1:5,000 and below, however, histidine exhibited a moderately inhibitory effect on the amplitude of contraction and the tonus of the intestine, lasting from one to several minutes. In a dilution of 1:500 complete inhibition and loss of tone resulted. The pH of 7.6 of the oxygenated Ringer-Locke solution was altered, however, to a pH of less than 6.0 by the addition of the amount of amino acid necessary to make a dilution of 1:500. These paralytic effects of high concentrations of histidine were readily terminated by washing out the amino acid and restoring the normal bath fluid.

DISCUSSION

It is apparent from the results presented above that the reduction in volume and acidity of gastric secretion in response to food and histamine reported by certain clinical investigators to occur after histidine treatment has not been corroborated in dogs. Indeed, two of three pouch animals and one of two gastrotomized dogs showed an increased and prolonged gastric secretory activity during and for variable periods after histidine injections. The limited number of experimental animals, however, does not allow the conclusion that the amino acid was the direct cause of these secretory changes. If histidine should prove to be the cause, it is not clear why the effect is inconstant, nor is it evident why parenteral histidine should produce this effect in dogs on diets high in adequate protein and therefore high in this amino acid.

Nearly every amino acid has been investigated for its effect on the secretion of gastric juice. The most comprehensive work is that of Ivy and Javols (8) who used twenty pure amino acids in their investigation. Of these, twelve were active, but only when administered orally in relatively large doses. None of them was active in the sense of "gastric secretin" and all were ineffectual when given subcutaneously. Their experiments, however, were acute ones calculated to elicit immediate secretory responses and therefore not designed to detect any such histidine effects as might alter the response to standard food and histamine stimuli.

The results of the in vitro experiments recorded above are confirmatory of the findings of Hirschfelder and Cantwell (7). In addition, these authors have proven that any discernible histidine action is definitely due to pH alterations.

While realizing the difficulty in transferring data obtained in animal experiments to clinical problems, the authors feel that the results reported here afford no support for the therapeutic claims made for this amino acid in the treatment of peptic ulcer in man.

SUMMARY

The effect of intramuscular histidine on gastric secretion was studied in dogs with accessory stomachs

and in gastrostomized preparations. In vitro experiments were performed to determine the action of this amino acid on intestinal tone and motility.

Histidine did not decrease the volume or acidity of gastric secretory response to either food or histamine stimulation. In two of three pouch dogs and in one of two gastrostomized dogs there occurred a prolonged and increased secretory response coincident with histidine administration. In organ baths, histidine in physiological concentrations had no effect on the tone or motility of segments of small intestine. The data presented in the above experiments offer no support for the therapeutic claims made for histidine in the treatment of peptic ulcer in man.

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The Use of a New Antispasmodic Drug in Gastro-Enterology

A Preliminary Report

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IN all gastric diseases the symptoms are more or less similar, and appear in the form of heartburn, sour eructation, nausea, vomiting, etc. The outstanding complaint, however, which causes the patient to consult a physician for relief is pain. The pain may come as a mild discomfort or pressing feeling in gastric disorders, a cramp-like pain associated with diarrhea or constipation in intestinal disorders, or a sharp and cutting pain in the right upper quadrant in disorders of the gall bladder. Oftentimes, the pain is not definitely localized, but extends over the entire region of the umbilicus.

Aside from making a provisional diagnosis based on the clinical history and physical findings, or a complete study of the case by X-rays or other laboratory examinations, it is obvious that it is the duty of the physician to consider the welfare of his patient, and give him immediate relief of his pain. Numerous drugs are prescribed for this purpose, various derivatives of Belladonna being most frequently used.

Belladonna contains an active principle in the form

of an alkaloid known as atropine which is insoluble in water. The sulphate of atropine is soluble and is the salt most commonly used. Although this drug relieves the pain, there are certain unpleasant physiological setbacks connected with it, such as flushing of the face, inhibition of the salivary secretion, and dilatation of the pupils, produced in part by a depressant action on the endings of the oculomotor nerve in the iris. Belladonna also quickens the pulse, and may produce an increase of arterial pressure.

In my own practice, I discontinued the use of Atropine Sulphate and Extract of Belladonna, and, in addition to other new antispasmodic drugs, used Tincture of Belladonna, since the individual dose can be obtained more easily without marked unpleasant side effects, by increasing or decreasing the number of drops.

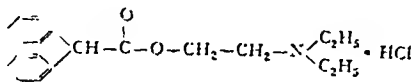
Due to its unpleasant setbacks, the general use of atropine as an antispasmodic was impeded, and numerous efforts were made by various pharmaceutical

houses to find a substance which would give the same antispasmodic effect without the undesirable side-effects.

Recently, a new drug was placed on the market, which I have been using in my practice. I have made a study of this drug on a number of my patients, and shall give herein a preliminary report of my findings from a clinical point of view.

Pharmacological studies of this drug have been made by Dr. Rolf Meier (1) in Europe, and by Drs. Johnson and Reynolds (2) in this city, and below I shall give a summary of their findings, so that the physician may understand the exact status of the pharmacological action of this drug.

According to Meier, this new synthetic preparation, Diphenylacetyldiethylaminoethanolester-hydrochloride has the following structural form:



This preparation is a white crystalline material, readily soluble in water, and is stated to have a melting point of 112 to 114 C. The colorless aqueous solution can be sterilized without any alteration of its properties, and is stable. Dr. Meier claims that this substance belongs to a class of basic esters all characterized by the presence of the diphenylacetyl group, which, by recent pharmacological studies, were found to possess excellent antispasmodic action. The diethylaminoethylester has been claimed by him to be the most satisfactory representative of this group, and was, therefore, selected for therapeutic purposes.

Pharmacologically speaking, the most significant quality of this new compound is that it happens to have pronounced muscular action, as well as a neurotropic effect on the ends of the parasympathetic nerve, when tested on the isolated intestine of the rabbit.

To understand the importance of this fact, it may be recalled that the so-called "antispasmodic" drugs, supposed to give relief in various pathological states characterized by hypertension or increased irritability of the autonomically innervated organs, are theoretically divided according to the points of attack. Thus, in pharmacology, those drugs causing chiefly relaxation of the smooth muscles, after their irritation by specific muscle stimulants like barium salts, are separated from those antagonizing the spastic effect of a number of drugs which stimulate the autonomic parasympathetic nerves, controlling the function of smooth muscles.

In order to determine the pharmacological activity of this substance, Dr. Meier made a number of experiments comparing it with well-known preparations possessing similar properties such as Atropine and Papaverin. The study was made on an isolated segment of the intestine of the rabbit. Of great importance when determining the antispasmodic effect of a given preparation is its action on the intestines in which spasms have been produced artificially by administration of neurotropic or musculotropic stimulants. In the customary manner the neurotropic spasms were produced with acetylcholine while for the induc-

tion of musculotropic spasms barium chloride was used.

In the first set of experiments on isolated intestine of rabbit, spasms were induced by acetylcholine and a comparison of the action of the product with atropine sulphate was made. The result was that the spasm relieving action of this new drug set in following administration of a dose 20 times as large as the dose of atropine required to obtain the same effect. From these experiments it is apparent that the drug has a pronounced antispasmodic action on spasms of neural origin.

In the second set of experiments on isolated intestine of rabbit, musculotropic spasms were induced by barium chloride, and a comparison of the action of the product with Papaverine was made. The following results were obtained: With Papaverine the complete relief from intestinal spasm can only be obtained in the most favorable cases by the use of concentrations of from 10^2 to 5×10^3 , while on the other hand, the new product produces definite results in concentrations of 10^2 , proving that its musculotropic action is at least equal to that of Papaverine. Furthermore, it is important that when the BaCl_2 spasm has been relieved by the drug the spontaneous movements of the intestines are almost completely reestablished, while following the use of Papaverine in doses required to obtain the same effect, complete paralysis generally sets in. These experiments prove that on the isolated intestine of the rabbit the drug combines the paralyzing effect on the parasympathetic nerves with the complete desirable musculotropic action of Papaverine.

A study of the effect of the drug on the iris was also made, and the following results were obtained: A 1% solution on the cat's eye produces only a very slight transitory dilatation of the pupil while dilatation produced by atropine in concentrations as low as .001% is clearly noticeable. The action of atropine is, therefore, 1000 times stronger than that of the drug when tested on the cat's pupil.

Likewise the effect of this drug on the salivary secretion in rabbits following pilocarpine stimulation is much less than that of atropine. It is not possible even with sublethal doses of the new compound to obtain a complete inhibition of salivary secretion.

The pharmacological study of the drug was made in this country by Drs. Johnson and Reynolds (2). In their work they were concerned with three aspects of its pharmacodynamic action, namely, its toxicity, its effects upon the circulatory system and respiratory movements, and its antispasmodic properties on uterine muscle.

Toxicity of the Drug:

The study was made on rabbits and cats and it was found that it is moderately toxic when given intravenously, but intraperitoneally or intramuscularly it is not toxic except when given in excessive amounts. It does not have any appreciable cumulative action and it rapidly loses its toxic properties when injected into the blood stream.

Circulatory and Respiratory Effects:

Experiments were performed on cats, and administered by routes other than intravascular, had no marked circulatory effect and was free of any measurable action on respiratory movements, even when large

amounts of the drug were administered. Intravenously, its effect on blood pressure is depressing but evanescent.

Antispasmodic Action on Uterine Muscle:

(a). *Antagonism to posterior pituitary extracts:* This drug was found to reduce but not abolish the uterine spasms induced by the oxytocic action of pituitrin. This antispasmodic action of the drug was observed to persist for more than an hour, but not for several hours.

(b). *Antagonism to pilocarpine.* The drug was found to inhibit the persistent elevation of tone in uterine muscle which normally follows the injection of pilocarpine. In this respect, the drug is not as wide in its scope of action.

(c). *Antagonism to calcium salts.* It inhibits spasms of the general uterus of the unanesthetized rabbit produced by calcium lactate.

In summary, it may be said, that Johnson, Reynolds and Meier found that this new substance is a drug having pronounced antispasmodic properties. In contrast to atropine, those parasympathetic paralyzing actions which in humans are the cause of unpleasant by-effects, especially pupillary dilatation and inhibition of salivary secretion, are much less pronounced with this drug. Besides this neutral action, it also exhibits the typical muscular action inherent to papaverine.

Dr. U. Salow (3) made a clinical study of this new preparation on 51 patients, 22 of which were gastro-intestinal cases. He obtained good results in 42 of these cases, but no results in the remaining 9 cases.

The preparation was well tolerated by the patients, no matter by which method it was administered. Complaints of unpleasant side-effects were never received, and only a few patients who had received the preparation over a long period, mentioned that they had occasionally felt slight dryness in the mouth.

Dr. F. Nagel of the famous Von Jagic clinic in Vienna (4) also made a clinical study on 56 patients, 33 of which were gastro-intestinal cases. He obtained good results in 27 cases, moderate results in 14 cases, and no results in the remaining 15 cases. He also observed that the side-effects, such as dryness of the mouth, dilatation of the pupils of the eyes, and palpitation of the heart, were not present.

In my own study of this drug in 24 gastro-intestinal cases, covering a period of more than a year, (preliminary report of which is given below), I was concerned mainly with the following: (1) The presence or absence of the side-effects which usually accompany atropine, such as dryness of the mouth, dilatation of the pupils, and circulatory disturbances; (2) its immediate effect on pain.

It is understood that this product was not given alone, but in conjunction with my usual medication, except that this drug was substituted for Tincture of Belladonna.

The cases consisted of the following: eleven duodenal ulcers, one gastric ulcer, one diverticuli of the duodenum, one cardiospasm, three cholecystitis, five colitis (spastic of mucus), one hyperacidity and one acute intestinal obstruction.

The results may be summed up as follows:

1. All the patients were free of side-effects, such as dryness of the mouth, dilatation of the pupils of

the eyes, palpitation of the heart and irregular pulse.

2. No definite relief of pain was reported in the cases of cholecystitis. The results were poor because the pain was intimately associated with the inflammatory process rather than with a spasm, hence logically relief following the use of an antispasmodic could hardly be anticipated. No results were obtained in the cases of cardiospasm, because cardiospasm is a *misnomer* and is not a true spasm of the cardia.

3. Good results were obtained in the remaining cases. The patients were relieved of their pain, although this relief cannot be attributed entirely to the drug, since same was used in conjunction with other medication (diets, alkaline powders, etc.).

4. Excellent results were obtained in certain cases where hiccough was present. This complaint disappeared completely about twenty minutes after administering the drug intramuscularly.

5. There were no toxic effects, even when the drug was administered over a long period of time.

Case 1. Bleeding Duodenal Ulcer—R. R., female, 39. Gastric complaint: Pain two hours after meals, relieved by food and bicarbonate. Attack of *melena* in 1928. Recurrence in 1932, but no *malena*. Free of symptoms until spring 1937, when a second hemorrhage occurred. Roentgen-ray findings: Irregular duodenal bulb. Free HCl: 52; Total 75. Hospitalized and treated with diet, special alkaline powders and Trasentin tablets. Pain disappeared. No side-effects.*

Case 2. Pre-pyloric Duodenal Ulcer—M. S., male, 33. Gastric complaint: Abdominal pain for first time in 1927. Hemorrhage in 1929. Recurrence in 1934, and nearly every six months thereafter, usually in the spring and fall. Recently, recurrences more frequent, with loss of weight and occasional vomiting of blood. Roentgen-ray findings: Pre-pyloric and duodenal ulcer. Free HCl: 35; Total 70. Patient placed on medical ambulatory treatment, consisting of diet, powders and Trasentin tablets. Symptoms quickly disappeared, condition improved, and patient gained weight. No side-effects.

Case 3. Spastic Colitis—B. F., male, 38. Gastric complaint: Pain in epigastric region 3-4 hours after meals, usually along the transverse and descending colon. Roentgen-ray findings: No abnormal findings of stomach or duodenum. Twenty-four hour examination revealed all the barium evacuated. Barium enema showed spasticity throughout the descending colon and sigmoid. Sigmoidoscopic examination negative. Free HCl: 20; Total 46. Patient placed on a colitis routine, consisting of special diet, Kaolin powder and Trasentin tablets. Pain disappeared. No side-effects.

Case 4. Duodenal Ulcer—J. S., male, 24. Gastric complaint: Pain 2 hours after meals, relieved by alkaline powders or milk and cream. Roentgen-ray findings: Irregular duodenal bulb. Free HCl: 32; Total 54. Appendectomy was done in the fall of 1936, as it was believed that the complaint was due to a pathological appendix, but the symptoms were present even after the operation. Patient was hospitalized, and the routine treatment with Trasentin tablets was given. Symptoms disappeared, and there were no side-effects.

Case 5. Cholecystitis and Spastic Colitis—F. M., female, 44. Gastric complaint: Pain in epigastric region, also along the left upper and lower quadrants of the abdomen, usually $\frac{1}{2}$ hour after meals; also before and during bowel movement. Intermittent constipation and diarrhea. No vomiting and no loss of weight. Enemas had a tendency

*Side-effects: Dryness of the mouth, dilatation of the pupils of the eyes, circulatory disturbances such as palpitation of the heart and irregular pulse.

to aggravate the pain along the left lower quadrant of the abdomen. Roentgen-ray findings: No abnormal findings of the stomach or duodenum. Barium enema showed a spasticity throughout the descending colon and sigmoid. No visualization of the gall bladder. Free HCl: 62; Total 92. Patient treated with diet and Trasentin tablets. The abdominal pain did not disappear and the results were not satisfactory in this case. No side-effects.

Case 6. *Duodenal Ulcer*—Rev. E. Z., male, 45. Gastric complaint: Pain in the epigastric region radiating to the back, usually 1-2 hours after meals. Relieved by food and bicarbonate. Recurrences usually in the spring and fall. Roentgen-ray findings: Duodenal bulb irregularly filled. Free HCl: 55; Total 75. Patient placed on medical ambulatory treatment (diet, special alkaline powders and Trasentin tablets). Symptoms disappeared. No side-effects.

Case 7. *Penetrating Gastric Ulcer*—B. B., female, 49. Gastric complaint: Pain in epigastric region immediately after, or 2-3 hours after meals, radiating also to the back. The pain is gripping and burning in character, and remains until the patient is relieved by vomiting. The vomitus was previously only stained with blood, but lately contained pure blood. Recently, patient had pain immediately after meals, accompanied by hiccoughs. At first the hiccoughs came only intermittently, but later they became continuous. There were no hiccoughs when the patient did not take any food. She suffered with these symptoms for a period of two years, and they reappeared six months ago, and then three months ago, and lately became more frequent. Patient was hospitalized twice before reporting to my office, and was previously treated for cholecystitis. When patient came under my care, she had lost about 15 pounds. The roentgen-ray findings revealed a penetrating gastric ulcer on the posterior wall about 1½ inches below the cardia. Hospitalized for a period of three weeks, and fed through a tube. Trasentin tablets and ampoules were given, and later patient was placed on an ulcer diet. The hiccoughs and the vomiting stopped. Condition improved, gained weight, and recovered completely. No side-effects. Also no toxic effects when large dose of Trasentin were given.

Case 8. *Cardiospasm*—I. K., male, 44. Gastric complaint: Pressing feeling in the chest, and difficulty in swallowing. Roentgen-ray findings: Cardiospasm. Injections of Trasentin proved unsatisfactory, and the patient was treated by gastric feeding and dilatation by special dilating apparatus. The so-called cardiospasm is not a spasm of the cardia, but is more of a cardiologic in nature, with a disturbance in the opening and closing of the cardia. The Trasentin therefore, had no effect on this condition. No side-effects.

Case 9. *Cholecystitis*—M. Y., female, 56. Gastric complaint: During the past two years, patient had intermittent attacks of pain in the right upper quadrant of the abdomen, radiating to the right shoulder; also attacks of hiccoughs. Roentgen-ray findings: Examination done elsewhere, revealed a faint visualization of the gall bladder. Patient was placed on a special diet, and Trasentin tablets were given. The pain was reduced, but did not disappear entirely, and the hiccoughs disappeared completely. No side-effects.

Case 10. *Duodenal Ulcer*—J. G., male, 42. Gastric complaint: Pain in epigastric region 2-3 hours after meals, relieved by food and bicarbonate; also night pain. Free HCl: 50; Total 66. Roentgen-ray findings: Irregular duodenal bulb. Patient was hospitalized, and treated with ulcer diet, and Trasentin tablets. The symptoms disappeared and he gained weight. No side-effects.

Case 11. *Spastic Colitis*—Dr. A. G., male, 41. Gastric complaint: Pain along the descending colon, usually with bowel-movement. First time in 1931. Intermittent diar-

rhea and constipation. Barium enema shows spasticity throughout the colon, particularly the descending colon. Patient placed on soft diet and Trasentin tablets. Symptoms disappeared, the bowels became regular. No side-effects.

Case 12. *Duodenal Ulcer*—J. M. T., male, 38. Gastric complaint: Pain in the epigastrium 2-3 hours after meals, relieved by hot drink or bicarbonate. Same complaint a year ago. Free HCl: 35; Total 47. Roentgen-ray findings: Duodenal ulcer with niche on the inner border. Hospitalized and treated with ulcer diet and Trasentin tablets. Symptoms disappeared. No side-effects.

Case 13. *Duodenal Ulcer*—J. B., male, 54. Gastric complaint: Pressing feeling and fullness in the chest and epigastric region. No definite relation to meals, and usually more aggravated in the morning. Same complaint 15 years ago, 8 years ago, and again during the past year. About a year ago a general practitioner diagnosed the case as coronary artery disease, although the electrocardiograph was negative. Roentgen-ray findings: Irregular duodenal bulb, with a niche at the base of the inner border of the bulb. Also diverticuli along the descending colon. Free HCl: 27; Total 52. Patient was hospitalized and treated with an ulcer diet and Trasentin tablets and ampoules. Symptoms disappeared. No side-effects.

Case 14. *Duodenal Ulcer*—S. K., male, 34. Gastric complaint: Pain along the umbilical region and the right upper quadrant of the abdomen, usually after meals, also night pain. Relieved by food and bicarbonate. Appendectomy in 1931 but patient had the same recurrences in 1933, 1935 and 1936. Roentgen-ray findings: Irregular duodenal bulb. Patient was hospitalized and placed on an ulcer diet with alkaline powders and Trasentin tablets. Symptoms disappeared. No side-effects.

Case 15. *Mucous Colitis*—M. D., female, 43. Gastric complaint: Discomfort and annoying feeling over the entire abdomen. No relation to meals, but associated with the bowel movement. Bowels loose, with large amount of mucus. Barium enema revealed very irritable and spastic colon. Patient was placed on a colitis diet, with anti-diarrheal powders and Trasentin tablets. The diarrhea stopped, the pain disappeared, and there were no side-effects.

Case 16. *Duodenal Ulcer*—B. W., female, 44. Gastric complaint: Cramps 3-4 hours after meals. Relieved by food and bicarbonate. Heartburn. Patient previously treated for an ulcer. Roentgen-ray findings: Irregular duodenal bulb. Cholecystographic examination negative. Free HCl: 35; Total 60. Patient was placed on a ambulatory treatment, and alkaline powders and Trasentin tablets were given. Symptoms disappeared and there were no side-effects.

Case 17. *Duodenal Ulcer*—J. M., male, 41. Gastric complaint: Pain in epigastric region two hours after meals. Relieved by alkaline powders and food. Severe night pain and heartburn. Roentgen-ray findings: Irregular duodenal bulb. Intermittent recurrences for past ten years. Last attack quite severe, and patient was therefore hospitalized and treated with the drip method. Trasentin tablets and ampoules. Symptoms disappeared entirely. No side-effects.

Case 18. *Duodenal Ulcer*—L. E., male, 39. Gastric complaint: Discomfort in the epigastric region about 1-1½ hours after meals. Relieved by alkaline powders and food. Intermittent recurrences for past few years, in the spring and fall. Roentgen-ray findings: Irregular duodenal bulb. Free HCl: 30; Total 60. Patient was placed on a diet, alkaline powders and Trasentin tablets. Symptoms disappeared and there were no side-effects.

Case 19. *Hyperchlorhydria*—M. L., male, 21. Gastric complaint: Pressing feeling and fullness in the epigastric

region and the chest. Relieved by belching. Occasional hiccoughs, heartburn and sour eructation. No abdominal pain. Roentgen-ray findings: Fluoroscopically, pylorospasm for 15 minutes; otherwise, negative. Free HCl: 57; Total 70. Patient was treated with alkaline powders, Trasentin tablets and ampoules. Symptoms disappeared. No side-effects. Patient was X-rayed again at a later date and no pylorospasm present.

Case 20. *Mucus Colitis*—L. B., female, 35. Gastric complaint: Pain over entire region of the abdomen, particularly with bowel movement. Intermittent constipation and diarrhea, and mucus with the bowels. Proctosigmoidoscopic examination revealed a large amount of mucus present in the rectum and sigmoid. Barium enema examination showed spasticity throughout the colon. Patient was placed on a colitis diet and Trasentin tablets. The bowel movement was regulated, the pain disappeared, and there was less mucus with the bowels. X-ray examination done at a later period, revealed less spasticity throughout the colon. No side-effects.

Case 21. *Acute Intestinal Obstruction*—R. M., female, 40. Gastric complaint: Acute cramps over the entire abdomen, particularly in the right upper and lower quadrant. Cholecystectomy and appendectomy July 11, 1936, and numerous small biliary calculi found in the gall bladder. Patient felt well for about 18 months, but then suddenly was seized with severe cramp-like pains in the lower right quadrant of the abdomen. The cramps came at intervals of every five minutes. Patient vomited fecal matter. Diagnosis of acute intestinal obstruction was made, and 1½ c.c. Trasentin ampoule was given to relieve the pain. Pain subsided after a period of about 20 minutes. Patient was removed to the hospital and operated on, releasing a band which had formed across the small intestines.

Case 22. *Cholecystitis*—E. W., female, 52. Gastric complaint: Occasional pain during the past ten years in the right upper quadrant. Attack with jaundice eight years ago. Five years ago another attack, but no jaundice. Lately the attacks became more frequent. Roentgen-ray findings: G.I. Series: Negative. No visualization of the gall bladder. Patient was placed on a gall bladder diet and Trasentin tablets. The pain disappeared, and her condition improved. No side-effects.

Case 23. *Diverticuli of the Duodenum*—A. A., female, 32. Gastric complaint: Pain commenced at the age of

twelve. Intermittent pain throughout adolescence, coming at more frequent intervals as she grew older. Patient was X-rayed in 1927, and the examination revealed diverticuli of the duodenum. Was operated on that same year, and a superior and inferior diverticuli with inflammatory reaction was found distal to the pyloric ring. A gastroenterectomy was done with no exclusion of the pylorus. Patient felt well for a period of five years, then since 1936 recurrent attacks of pain. X-ray examination revealed the barium passing through the new opening, but also some passing through the pylorus. Patient was hospitalized and placed on an ulcer diet, Trasentin tablets and ampoules. The pain disappeared and her condition improved. No side-effects.

Case 24. *Duodenal Ulcer*—E. B., female, 28. Gastric complaint: Pain in the epigastric region, 2-3 hours after meals; also night pain. Relieved by food and bicarbonate. Same complaint a year ago. Roentgen-ray findings: Irregular duodenal bulb. Patient was placed on an ulcer diet and Trasentin tablets. Pain disappeared and the condition improved. No side-effects.

SUMMARY

A new antispasmodic drug was used in 24 G.I. cases. All were free of side-effects such as dryness of the mouth, dilatation of the pupils and palpitation of the heart. Relief of pain was obtained in most cases after administering the drug. Also, particularly good results were obtained in cases where hiccough was present.

The above is only a preliminary report, and at a later date the study of the drug will be continued, along the following lines:

1. Its immediate effect in attacks of biliary colic.
2. Its effect in cases of pylorospasm.
3. Further study in cases of spastic colitis.

I wish to express my gratitude to Mr. L. T. Hilcorn, President of Clay-Adams Co., for his kind cooperation in the development of my tube.

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Editorials

FACTORS WHICH INFLUENCE THE REGENERATION OF BLOOD FOLLOWING HEMORRHAGE FROM PEPTIC ULCER

MANY clinicians have accepted as more or less inevitable the prolonged convalescence which often follows moderate or severe bleeding from peptic ulcer. One of the most significant factors contributing to the slow recovery of the patients is the delay in restoration of the blood to normal values which is due, in many cases, to depletion of stores of iron as a result of chronic loss of blood. For many years the treatment of patients with bleeding peptic ulcer has consisted principally of a few days of starvation followed by a very limited intake of food and the frequent use of alkalies, all of which appears now in the light of our present knowledge to have tended further to retard convalescence.

If recovery from bleeding is to be rapid it is essen-

tial to have available in the diet in abundant quantities such substances as iron and protein, which are necessary for regeneration of the blood. Consideration also must be given to those factors which may influence the absorption of iron and other essential substances from the gastro-intestinal tract. Studies within the past few years have made available information about these factors which should prove of great practical value in reducing the usual period of disability from bleeding.

Whipple and his coworkers have shown clearly that foods such as liver, kidney, gizzard, spleen and pancreas, are the most potent in stimulating the production of new hemoglobin in dogs rendered anemic by bleeding. Of various inorganic elements, iron was found to be the most effective in the production of new hemoglobin.

Other important factors in maintaining the blood at normal levels include the intrinsic substance of

Castle, certain amino-acids, copper, vitamin C, and some components of the vitamin B complex.

Within the past two years Meulengracht has reported the results of his use of "treatment with food" as contrasted to "treatment with starvation" of patients with bleeding from ulcer. Using a full purée diet and iron medication he reported not only a shorter convalescence from the period of shock but a considerably reduced mortality among those patients with actively bleeding peptic ulcers. These observations have done much to stimulate others to use this form of treatment. If clinical experience should show that this method of treatment is safe in most cases, much may be accomplished in the future in shortening the period of convalescence from bleeding.

Recent emphasis on the rôle of the gastro-intestinal tract in the predisposing to or conditioning of deficiency diseases has focused our attention on the importance of such a factor as gastric acidity in the utilization and absorption of the products of digestion. The impairment of utilization of iron in some patients with achlorhydria has been recognized for some years and has led to the very interesting observations of Kellogg and Mettler that alkaline therapy used in the treatment of peptic ulcer apparently interferes with the utilization of dietary iron. These observers made careful studies of the blood of four patients with anemia secondary to prolonged loss of blood from peptic ulcer. Observations were made of the changes which may take place in the formation of blood as a result of the administration of a diet rich in iron during periods in which the upper part of the gastro-intestinal tract was made alkaline by a modified Sippy regimen and after the alkaline therapy was discontinued. It was demonstrated that a diet rich in iron had practically no effect on the formation of hemoglobin during the period of alkalization. However, after the administration of alkalis was stopped, there was a marked improvement in the blood, with reticulocytosis and a subsequent increase in the concentration of the hemoglobin. The increase in number of erythrocytes in the blood was comparable to that produced by adequate therapy with inorganic iron. During periods of administration of a diet rich in iron and alkalization in which the concentration of hemoglobin did not rise appreciably, there was observed a slight but consistent increase in the number of erythrocytes in the blood, the result, presumably, of the absorption of some substances necessary for the formation of cell stroma or for the maturation of erythrocytes. The possibility that achlorhydria or alkalization may significantly interfere with absorption of other essential hematopoietic factors is indicated by the studies of Einhauser, who has pointed out that utilization of test doses of vitamin C by patients with achlorhydria is disturbed because of inadequate absorption. These observations on the influence of alkalization of the upper portion of the intestinal tract on the absorption of iron and vitamin C suggest that patients with anemia resulting from bleeding are likely to remain anemic until alkalization is discontinued or until large doses of inorganic iron, and in some cases perhaps vitamin C, are given.

As a result of these considerations, in the treatment of patients who have recently bled from peptic ulcer it seems wise for the physician to remember those foods which have been shown to be potent and essential in the regeneration of the blood, to see that the

patient receives them in adequate amounts in a form compatible with comfort and rapid recovery and, lastly, to take into consideration those conditions which may interfere with the function of the gastro-intestinal tract, particularly with regard to changes in its chemical reaction following the administration of alkalis.

Dwight L. Wilbur, San Francisco, Calif.

IS THERE A TREATMENT FOR HEPATIC INSUFFICIENCY?

IN spite of a growing knowledge of liver disease the physician is still powerless to combat severe hepatic damage. Furthermore, there has been no reliable method of differentiating between a liver damage from which recovery may be expected, and one which will lead to death. However, Shapiro, McNealy and Melnick (1) in a study of 700 jaundice cases found that a prognosis could be based on the changes in the Ivy bleeding time, which reflects the hemorrhagic tendency in these patients. If the bleeding time became progressively more prolonged, or failed to return to normal after a week of Viosterol administration, then death from hepatic insufficiency or hemorrhage was almost certain, in spite of all available measures taken to aid the patient. This work has recently been confirmed in detail by Boys (2).

Still another possible means of prognosis has been developed recently, based on the cholesteryl ester level of the blood. Epstein and Greenspan (3) determined the cholesterol partition of the blood in over 500 patients with liver disease. In biliary obstruction they found the cholesteryl esters to be elevated, paralleling the degree of icterus. In parenchymatous degeneration, on the other hand, the cholesteryl esters fell in proportion to the severity of the hepatic involvement. In severe yellow atrophy the esters even disappeared from the blood. The determination of cholesteryl esters, they state, has helped materially as an aid in prognosis. Patients with an apparently hopeless clinical outlook and rising ester levels have improved, and conversely, those with apparently mild disease and steadily falling ester levels have gone on to yellow atrophy of the liver and death.

Although methods which apparently permit a more dependable prognosis, are therefore now available, there is as yet no treatment which can arrest the progress of hepatic degeneration. However, the association of decreasing cholesteryl esters with ultimately fatal hepatic insufficiency in clinical cases, may provide a useful lead to a rational therapy. It has been known for many years that depancreatized dogs maintained on a diet without raw pancreas, develop a progressive fatty degeneration of the liver, resulting eventually in death. Chaikoff and Kaplan (4) have shown that this liver damage is associated with a progressive fall in cholesteryl esters of the blood with a correspondingly increased deposition in the liver. This alteration in distribution of cholesteryl can be prevented by the inclusion of raw pancreas in the diet of these animals. What is more important, after the condition is far advanced, the administration of raw pancreas will rapidly restore the normal cholesteryl partition, and relieve the hepatic damage (5). It has been shown by Best and his co-workers (6) that the active constituent of raw pancreas is choline. Choline

is easily available, it is active by mouth, and comparatively non-toxic. One wonders whether it may not be of value in treating clinical liver damage.

This is not the only new possibility in the treatment of these patients. For years, Sato, a Japanese worker, has claimed that an extract of the liver is able to protect the liver from various hepatic poisons. Nothing, however, has been done elsewhere along this line until recently, when Forbes, Neale and Scherer (7) found that an extract of the liver was very effective in protecting the livers of rats against the degeneration produced by chloroform and carbon tetrachloride administered either subcutaneously or by inhalation. Recently Neale (8) has reported that the active constituent of these extracts is sodium xanthate, a purine compound. Unlike calcium, which has been reported to decrease the toxic symptoms produced by carbon tetrachloride and chloroform, without preventing liver degeneration (9), sodium xanthate is reported to prevent almost completely the degenerative processes in the hepatic cells. The compound is much superior to glucose in its protective action on the liver.

The above work with choline and sodium xanthate is still in the animal-experimentation stage. It is not necessarily true that choline, because it will benefit experimentally produced fatty livers in animals will also be effective in curing clinical liver damage. Furthermore, the evidence is not clear that sodium xanthate is as effective in curing as in preventing liver necrosis. Nevertheless, one can't resist the suggestion that these agents should be investigated with the view of providing a possible treatment for otherwise hopeless cases of hepatic insufficiency.

John S. Gray, Chicago, Ill.

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THE PHILOSOPHY OF THE DIABETIC LIFE

"MY diabetic physicians under the age of 40 have less than one-fourth the mortality of all my diabetic patients of similar age; those between 40 and 59 years have less than one-half the mortality as compared with their corresponding age group, and even above 60 the physician does better. My diabetic physicians are a living indictment of the inadequacy of my diabetic treatment. Must a diabetic person become a physician if he wants to live? If you do not think so, then you must teach the patient all the diabetic tricks of the trade." Thus spoke Joslin (1) recently in an article on protamine insulin. One of the "tricks" of the diabetic trade, not infrequently overlooked and neglected is teaching the patient the philosophy of the diabetic life.

Teaching the patient the right philosophy is the fundamental problem in the treatment of any chronic disease. This statement applies more specifically to diabetes mellitus than to other chronic diseases because of the better prognosis. Results of treatment of this condition are dependent upon a faithful continuity in details of treatment but unless the diabetic

patient develops a desirable philosophy, long time control of the disease is seldom consistent. There is an obvious need at the present time to regard the problem of diabetic treatment in a broader sense, to emphasize this apparently abstract phase of diabetic management. Joslin's statement affords abundant proof of this need.

Just what is this diabetic philosophy? It is a state of mind, a way of looking at the present and future and a practical understanding of the principles and details which underlie successful diabetic control. In the words of Osler it is "A Way of Life."

The physician who teaches this philosophy must be first acquainted with the fact that the diabetes of today is a "new diabetes." Joslin is responsible for the term "the new diabetes," and there are ample reasons to justify its use. Outstanding among them are the status of the adequately treated diabetic child, the lengthening of life of the diabetic from an average of a little over six years to almost 16 years, the practical disappearance of diabetic coma as a cause of death and the appearance of cardio-vascular complications as an increasing factor in mortality. The physician must also realize that the "new" diabetic child grows up, goes places and does things. He engages in athletic activity, plans his life work, gets married and perhaps has a family, and if he has been properly informed does not marry another diabetic or into a diabetic family. It should be obvious to the physician that such a person is exposed to the same physical and psychic traumas as his non-diabetic contemporaries, but with this difference, that these traumas frequently precipitate diabetic emergencies. Training the patient to meet these emergencies as they arise or to anticipate them is the duty of the physician.

The physician when he attempts to teach the patient the proper philosophy must also appreciate the importance of other factors which influence success or failure. Most important are the character, mentality and psychic behavior of the individual. Of lesser importance are the patient's family, his friends and business associates, his physician and possibly of least importance the character of the diabetes.

The Patient—The foundation for a proper diabetic philosophy is eradication of fear in the patient, assurance that restoration of normal weight, strength and ability to resume his former economic and social position is practicable and that a normal life expectancy may be anticipated provided he learns to live the rules consistently. In the absence of diabetic complications he should be instructed that they will not develop in the presence of controlled diabetes. In a diabetes of long duration where complications already exist the patient not infrequently has consulted his physician because of them and may be discouraged to the point of doing nothing constructive. Such a person should be reassured there is reason to believe that further progress of his complications can be prevented by good diabetic control.

We see several different attitudes toward the disease among our diabetic patients. The most common is discouragement. The patient who shows this behavior needs to be convinced that the diabetic ideal can be realized. He must be encouraged to resume all activities consistent with his physical capabilities. There is a certain danger in a person of this type that he may permit the care of the diabetes to dominate

his life and activities to the extent of hampering his normal social and economic efficiency. Other patients show resentment because they have developed the disease. Still others assume an attitude of resignation. Another group of patients does not have sufficient respect for the disease, either because the disease is mild or because they have become so well on account of treatment that over-confidence develops to the point that they pay little attention to diet, insulin dosage or urine tests. How to teach these different types of individuals the proper respect for the disease and confidence in their futures will tax the art of the physician. Personal conferences, and group instruction are equally essential.

The Members of His Family—We feel that the best results in treatment are obtained if at least one member of the patient's family is given a practical knowledge of the disease and its control. Pity and sympathy for him should be prohibited. Having a controlled diabetes is no excuse to shirk necessary duties and responsibilities. A physical inferiority complex can develop easily when given a little encouragement. A diabetic child should not be regarded or treated by members of his family as a sick child but should be disciplined in the same way as any other child. He should be trained as he grows older to assume more and more the responsibility for his own care.

His Friends and Business Associates—It is our opinion that for the most part it is a good policy for diabetics not to reveal to other than members of their immediate family the fact that they have diabetes. This prevents the patient being catalogued by his friends or acquaintances as a different or queer person and in many instances avoids an unfavorable appraisal by his employer of his economic value. He also saves himself the embarrassment of answering needless questions from thoughtless persons, such as, "aren't you afraid of forming a habit of taking those insulin injections?", "will you have to take them the rest of your life?", and others in similar vein. These experiences tend to put the patient on the defensive and are apt to break down his morale. By not publicizing his condition he may avoid also the experience of receiving and wondering about the propaganda of diabetic "cures." It is pretty well established as a fact that the names and addresses of diabetic patients are frequently sent with the best of intentions to quack drug manufacturing companies by the friends of the patient.

The Physician—There is yet a necessity for a considerable amount of education of the members of our profession. Some physicians are still thinking in terms of the diabetes of 1921. There are even a few who still advise patients not to take insulin. In this group archaic diet slips dispensed by drug manufacturing houses are still being handed to patients. We need to set up in our own minds higher standards of health and ideals of treatment for the patient, if we shall hope to instill in the patients' minds these same standards.

The Character of the Disease—The character of

the diabetes has relatively little to do with the attainment of the diabetic ideal. The establishment of the proper diabetic philosophy is the important factor. It should be born in mind that the preceding discussion applies to individuals who have only recently developed diabetes and not to the group of persons who have had an uncontrolled diabetes for a number of years and have developed serious complications.

With all these factors in our minds and gradually creating an understanding of them in the mind of the patient we must carry out the technical training. The primary principle of this training is the necessity of making it practicable for the patient to control the diabetes under widely different environments of living and working. Unless this principle is permitted to dominate the program we shall fail in our efforts to teach the patient the proper philosophy.

The technical education should consist of dietetic arithmetic, urine tests and administration and adjustment of the insulin dose. Food values should be learned until they are as usable as the multiplication table. Diet calculation should be practiced until it is possible for the patient to calculate a meal in from 2 to 3 minutes. Food should be weighed at home to keep the eye in training in order that when the patient is away from home he can visualize food portions accurately. The patient should be made to regard the making of urine tests and the taking of insulin in the same light as the daily routine of brushing the teeth or bathing. The adjustment of the insulin dose with variations in physical activity or infection should be taught until the patient develops what we like to call an "insulin consciousness." By this we mean that he should develop the habit of stopping a moment to think before taking insulin whether or not, for example, he plans to do extra work or take additional exercise that particular day.

We have spoken before of the danger of some people becoming slaves to this routine and permitting it to occupy too much of their time and thought. An hour daily is ample time for these duties and many expert persons use less but it requires patience and systematic planning to develop this degree of efficiency. A cheerful acceptance of the situation is the most desirable attitude. It can be pointed out to the patient, however, that there is a peace of mind that comes to the patient who knows every day the status of his diabetes and who is therefore ready for all emergencies.

Equipped with practical information which he uses each day, free from fear of diabetes or his future, with no resentment over his lot, the diabetic is in the best possible condition for the realization of the diabetic ideal. Such a person cannot then be classified as a chronic patient. Diabetics attaining these ideals are about us on all sides. There should be more of them. There will be more of them when the members of the medical profession appreciate more keenly their responsibility in teaching the philosophy of the diabetic life.

Blair Holcomb, Portland, Ore.

Abstracts

MOON, VIRGIL H.

Shock, Its Mechanism and Pathology. Arch. Path., 24:5-642, Nov., 1937 and 24:6-794, Dec., 1937.

"Shock is a deficiency in the circulation, not cardiac and not vasomotor in origin, characterized by decreased total blood volume, decreased volume flow and by hemoconcentration." The author gives in general review the history of the concept of the phenomenon of shock and critically analyzes the many factors, experimental and clinical, known today that have tended slowly to unravel the mystery of this confused subject. He has tried to correlate logically these different factors and place them in a composite interrelated whole—which he expresses briefly in the above quoted definition.

There are certain features of shock now generally accepted to be fundamental; namely, that the heart is not primarily at fault, that the origin does not lie in the vasomotor system, that there is a decrease in the total blood volume and an increase in the concentration of the blood, and that the volume flow of arterial blood—the volume output of the heart per minute—is markedly decreased. Other features not fundamental are regularly associated with shock: namely, anoxemia, lowered alkali reserve (except in shock following intestinal obstruction), lowered basal metabolism, decreased blood chlorides and increased lactic acid, glycogen and nonprotein blood content. Other features are variable: there are variations in the white blood cell count, in temperature, in vomiting, diarrhea, and the presence of blood in vomitus and feces.

The pathologic changes seen in the viscera in all forms of shock, as studied by Moon and his associates, seem to be universally as follows: the superficial veins are collapsed and bloodless, the heart blood and that in large vessels and organs is dark, thick and unclotted. The surface of organs have a purplish cast, the serous surfaces are congested and cyanotic. There are ecchymoses and the cavities contain blood tinged fluid. The bowels are atonic, distended, the mesenteric vessels engorged. The mucosae are congested and edematous, often with ecchymoses. They resemble purple velvet. The lungs are mottled with congestion, the capillaries and venules dilated and packed with blood corpuscles. Capillary hemorrhages are numerous. Edema is present. The liver and kidneys are deeply congested. Blood drips from the cut surface. The spleen, however, contains less blood than normal. It is contracted and the cut surface dry. The heart is cyanotic in color, the vessels engorged. The ad-

renal glands show no special changes. The meninges are wet with occasional punctate hemorrhages.

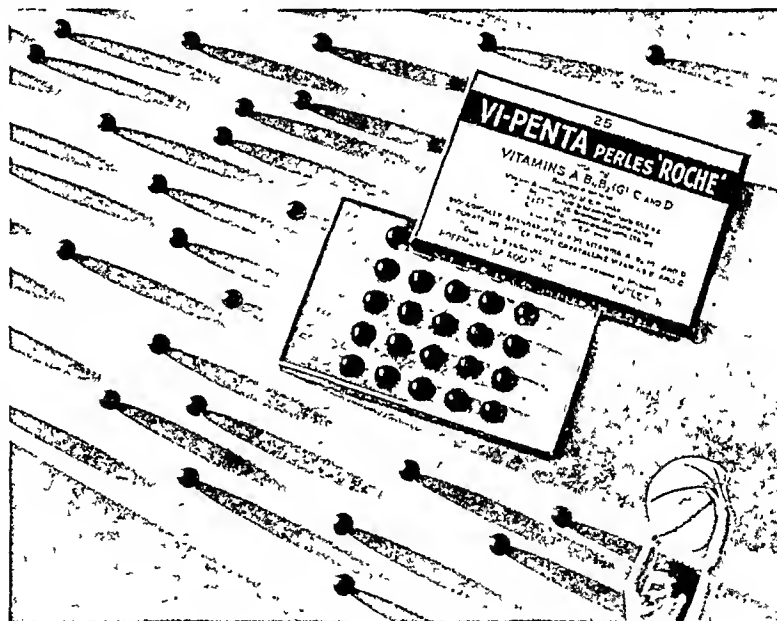
In several experiments the author injected a neutral solution of trypan blue intravenously into shocked animals. The colloidal dye is retained in the blood under normal conditions, but it passes into the tissues if the permeability of the capillary walls is increased. After death of the animals mucous and serous surfaces of the organs were found deeply blue, as was the fluid in the serous cavities.

The above pathologic changes were found in all cases of shock no matter how produced. They were interpreted

as indicating a loss of tonus of the capillaries and venules systemically, with stasis and increased vascular capacity of the vascular system. The edema indicated increased capillary permeability. Combined these factors account for the decreases in blood volume and for the hemoconcentration.

Shock may be differentiated from hemorrhage by the pathologic picture. The blood in the latter condition is diluted, the viscera are pale and ischemic, the tissues dry. In shock the blood is concentrated, the viscera are congested, the minute vessels engorged and the tissues are edematous. In man and in experimental animals the con-

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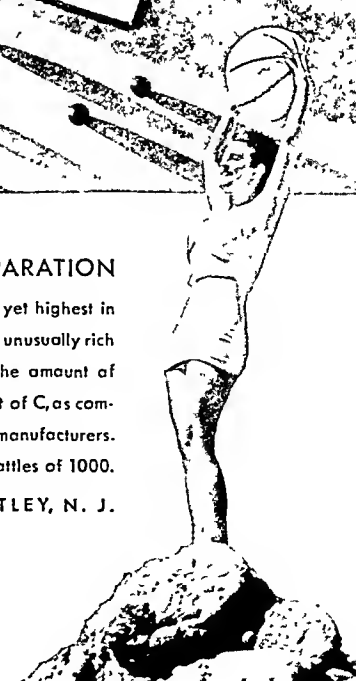


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gestion and edema of the lungs in shock from any cause often passes into true pneumonia, and may be the mechanism of terminal pneumonia in man.

The deficiency of the circulation in shock tends to become irreversible. If the blood pressure remains below 70 to 80 mm. of mercury for several hours the condition acquires a self-perpetuating quality and progresses. A stage is reached at which neither the body's physiologic reactions nor any known therapeutic measures are effective. A vicious circle is produced into which many diverse agents enter to continue the process. Starting the mechanism of shock with capillary atony (caused by

many and varied agents) the author establishes the sequence of events in the following order: capillary atony—reduced blood volume—reduced blood flow—deficient delivery of oxygen—tissue anoxia—deficient oxidation—acidosis—defective metabolism—capillary atony. The cycle may be initiated at other points than that of capillary atony. Hemorrhage may reduce blood volume sufficiently to produce anoxia, which, by causing capillary atony, will perpetuate the deficiency in the circulation. A loss of hemoglobin to 25 per cent may be restored immediately by transfusion, but with a few hours delay transfusion is ineffective; a n irreversible stage has been reached.

Finally, in resume the author discards various explanations of shock and gives the reasons therefore. The theory of vasomotor exhaustion is untenable; the heart, arteries and the nerve agencies controlling their action are not primarily involved. Acapnia does not explain and fat embolism is a different entity. Lowered alkali reserve is a result rather than a cause of the circulatory deficiency. Substances absorbed from injured tissues and many other agents—metabolic, chemical, bacterial, etc.—produce progressive circulatory deficiency by their effects on the minute vessels in systemic areas. Under the influence of these substances the capillaries and venules become atonic and dilated and their walls abnormally permeable to the fluids of the blood. This results in stasis and leakage of fluid from the vessels. It increases the volume capacity of the vascular system, reduces the total volume and the volume flow of the blood, increases its concentration and produces edema. Shock, in other words, like other conditions of disease, is accompanied by morphologic changes etiologically related to its mechanism of origin.

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BOYCE, FREDERICK FITZHERBERT AND
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"The Role of Liver Damage in the Mortality of Surgical Diseases."
South. Med. Jour., 31:35-39, Jan., 1938.

The importance of the liver as a site of medical or surgical disease is quite well recognized. Consideration of it as in the background of every surgical disease is a new conception and suggests the advisability of routinely determining the state of liver function preoperatively as one does the condition of the heart, lungs and kidneys. Post-operative liver deaths fall into one of the three groups. In the first place there are those presenting a toxic or infectious change secondary to the primary cause of illness. This is not due to a primary biliary deficiency. The second group includes the dramatic liver or liver-kidney deaths. The patient usually dies in twenty-four to forty-eight hours after operation with marked hyperphrexia or seven to fourteen days later with urinary symptoms predominating. These are true instances of liver failure and autopsy findings show degeneration or necrosis of the liver plus, in the delayed deaths, similar changes in the convoluted tubules of the kidney. It is probable here that previously damaged livers have no reserve margin of safety and when subjected to the additional strain of trauma and surgery fail in the normal function of detoxification, undergo necrotic change themselves and release increased toxic material into

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the circulation with subsequent kidney damage. The third group of cases which have the same pathological picture as just described are those associated with mechanical trauma to the liver as by stab or gunshot wounds. The clinical importance of this observation is that it is probably better to resect crushed areas than to risk hepatic necrosis.

Liver deaths similar to those just described have been demonstrated in toxic thyroid disease, intestinal obstruction, pancreatic disease, and ap-

pendicitis. It would, therefore, seem apparent that evaluation of liver function would be worthwhile if adequate tests were available. Blood cholesterol findings are relied upon by some but do not appear as satisfactory as the Quick hippuric acid test. Surprising evidence of liver impairment have been noted preoperatively in patients expecting an elective herniorrhaphy or interval appendectomy. Routine application of this test post-operatively as well as preoperatively would serve as an excellent index for the need of glucose which

is so valuable where liver function is diminished.

J. Duffy Hancock, Louisville.

FRAZER, E. B. AND MEEKER, WM. R.

"Regional Ileitis — Clinical Report of Two Cases." *South. Med. Jour.*, 31:152, Feb., 1938.

Regional ileitis is probably a clinical rather than a pathological entity. Any portion of the small or large intestine may be involved but the lesion is most common in the ileum. The pathological process while resembling a new formation is neither neoplastic nor due to any specific organism. The involved segment is greatly thickened, heavy and reddened, the lumen of the bowel is irregularly distorted and narrowed, the mucosa is subjected to a destructive ulcerative edematous process, the submucosal and muscularis coats show inflammatory, hyperplastic and exudative changes, the mesentery is still and there are frequent adhesions to neighboring viscera with possible fistulous communication.

It is difficult to assemble the symptoms into a definite clinical syndrome. There is usually fever, diarrhea without tenesmus, loss of weight, progressive anemia, pain and ileocecal tenderness. The stools may be mushy or liquid and may contain mucus, pus, or blood. Vomiting, cramps, and constipation will depend upon degree of obstruction present. X-ray examination is of great aid. A characteristic finding is the beaded string appearance of the involved segment.

The pre-operative diagnosis is frequently incorrect. While cures have been reported following simple exploratory laparotomies surgical removal of the lesion seems to be the method of choice. (Note: Ileocolostomy with division of the ileum when no fistulae are present is not discussed by the authors).

Two interesting successful cases treated by resection of the ileocecal coil are reported.

J. Duffy Hancock, Louisville.

RANKIN, FRED W. AND GRIMES, ALLEN E.

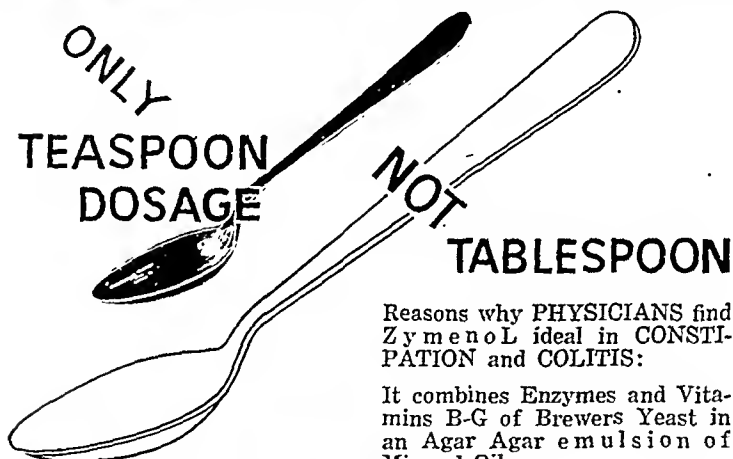
"The Surgical Treatment of Diverticulitis." *South. Surg.*, 7:1-15, Feb., 1938.

Diverticula occur in all portions of the gastro-intestinal tract from the esophagus to the rectum, but most frequently are found in the sigmoid colon. No adequate etiological explanation has been offered. It would seem, however, that from some unknown cause, probably congenital, a weakness exists in the intestinal coats and by reason of this a pouching of the coats takes place when any undue pressure arises. About five per cent of cases examined by barium enema will show diverticula,

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the vast majority of patients are beyond 40 years of age, and sex plays no part. The presence of diverticula causing no complaints is described as diverticulosis. With the onset of inflammatory changes the condition is designated as diverticulitis. Acute, subacute and chronic diverticulitis are considered to be fundamentally medical problems, and the complications of abscess formation, partial obstruction, massive hemorrhage, external or internal fistula, and associated malignancy essentially surgical.

Uncomplicated cases usually manifest themselves by some alteration in bowel habit frequently constipation alternating with occasional diarrhea. There is an associated variable degree of pain ranging from heaviness, fullness, or soreness to severe cramps; bleeding is rarely profuse and nausea, vomiting palpable mass, and stools of reduced caliber will be dependent upon the degree of obstruction present. Proctoscopic examination is often of great aid but the most accurate information is obtained from reliable roent-

genological studies. The principal findings are the rounded know-like projections from the lumen of the colon, spasm, and hypermotility. The relationship of cancer and diverticulitis is only coincidental and it must be remembered that diverticulitis with tumefaction may mimic cancer in its gross appearance. The diagnosis of the acute group perforating into the peritoneal cavity without abscess formation is quite difficult unless the previous presence of the diverticula is known. The condition is most frequently diagnosed as acute appendicitis or ruptured duodenal ulcer.

The type of surgical treatment indicated is determined by the nature of the complication requiring surgery. A single perforated diverticulum should be closed, drains packed around the involved area and a temporary colostomy done. Resection may be indicated in the perforating type which walls off, and forms an abscess which burrows to beneath the anterior abdominal wall, requires incision and establishes a fistula. Where obstruction is the main factor, where a large immobile mass is imbedded in the pelvis, a colostomy allowed to remain open for six to twelve months, during which time the Elliot treatment can be given, seems the best procedure to follow. If a vesicle fistula is present primary resection is not advisable. There should first be a colostomy and bladder treatments to clear up infection and inflammatory reaction.

Six illustrative cases are described.

J. Duffy Hancock, Louisville.

GAITHER, E. H. AND BORLAND, J. L.

Gastroscopic Studies. J. A. M. A., 110:436, Feb. 5, 1938.

The authors believe that reliable diagnosis in cases of gastritis can be made only on gastroscopic observations. History, roentgenograms, symptoms, and secretory studies have not proved sufficient. The impressions presented in this article are based on careful gastroscopic studies.

The normal gastric mucosa is unblemished, smooth, glistening, translucent and orange-red in color. In patients with dyspeptic symptoms or definite gastro-intestinal disease there are a wide variety of changes, apparently inflammatory in origin, but it has been impossible to establish criteria by which disease entities may invariably be recognized. The best working classification of gastritis is that of Schindler who divides it into three types, superficial, hypertrophic, and atrophic. In most gastritic stomachs the lesions seem active, the superficial and hypertrophic classes. In a small percentage the lesion seems atrophic and inactive.

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redness, injection hemorrhage and superficial erosions the authors term superficial gastritis. If there are edematous rugae with hemorrhage or injection and the changes appear to be more than superficial but not actually proliferative or hypertrophic, the term "inflammatory" has been used.

In the hypertrophic cases the inflammation is not the predominant feature, the mucosa appears nearly normal in color but is thickened, the rugae are large but not edematous, small warty

nodules are seen between the folds, and there are small patches of mucosal thickening. Two other types have been recognized, that in which active inflammation is less evident but the entire stomach wall is involved in small hemorrhages and erosions and those in which there is a well marked granular appearance in the preantral zone, localized on the anterior wall.

Gastritis frequently accompanies gastric or duodenal ulcer, but the severity of the ulcer is no index of the

degree of gastritis. The superficial inflammatory type predominates. The two diseases may be considered as distinct.

In the atrophic group, the mucosa looks thin and unhealthy with a network of blue veins. The rugae are usually absent, and the color is bluish gray in some cases and has a yellow tinge in others. Often there is superimposed activity. These cases do not conform to previous clinical suppositions. They do not seem to follow atony, achylia, flaccidity or body type. The most marked evidence of atrophy is found in pernicious anemia.

Francis D. Murphy, Milwaukee.

WILBUR, D. L. AND WASHBURN, R. N.

Functional or Nervous Vomiting.

J. A. M. A., 110:477, Feb. 12, 1938.

The authors review 140 cases recently seen at the Mayo Clinic in which a diagnosis of functional vomiting was made. Many of these patients had previously undergone surgical procedures without relief. Of the 140 patients, 112 or 80 per cent were females and 28 or 20 per cent were males. Eighty-nine or 64 per cent were between the ages of 20 and 40 years. Seventy-five per cent of the patients vomited daily and the remainder had periods of remission. Vomiting occurred within one hour after meals in most cases and the immediate inciting causes were eating, nervousness, worry, excitement or emotional disturbances. These patients were frequently free of other gastro-intestinal symptoms. In this series, 51 or 36 per cent had some form of epigastric distress and approximately the same number suffered from constipation. The frequent vomiting did not seem to cause emaciation. Only 31 or 22 per cent of the patients were in poor general condition. The most common physical finding was some form of pelvic abnormality and in 104 cases the patient was of the "nervous" type. Other characteristic features were the ability of the patient to reach a receptacle before vomiting, the lack of abdominal symptoms, and the desire of the patient to eat again immediately. In many cases no abnormalities were revealed on examination, but there was a history of pelvic discomfort and dysmenorrhea.

Psychotherapy is the most important type of treatment. In some cases "treatment by explanation" is sufficient. In severe cases complete rest, restriction of food and fluids by mouth and sedatives may be necessary for a period of time. Ninety-seven cases were followed for at least two years and in 50 per cent of them the vomiting stopped completely, in 16.5 per cent the vomiting decreased or recurred and in 33 per cent no relief was obtained. The immediate prognosis is good and it has been found better for males than

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Francis D. Murphy, Milwaukee.

PAVEL, I.

Jaundice Caused by Functional Obstruction. J. A. M. A., 110:566, Feb. 19, 1938.

The pathogenesis of jaundice, except the hemolytic type and that due to mechanical obstruction, is uncertain. It has been supposed by some to be due to

hepatitis, but no decisive proof supports this view. The author has concluded that in a certain number of cases jaundice is caused by a reflex spasm of the sphincter of Oddi, a functional obstacle.

This type of case is characterized clinically by persisting icterus varying in intensity, unimpaired state of health, and discoloration of the feces. The positive diagnosis is based on examination of the biliary excretion by the Melzer-Lyon test. It is assumed in the present investigation that the spasm of

the sphincter of the common duct may be produced by pathologic changes situated in a region comprising the duodenum, the choledochus, and the head of the pancreas as well as changes in the pericholedochal lymphatics caused by regional inflammation including inflammation of the gall bladder.

Evidences of hepatitis were found in some of the author's cases. The important thing is to ascertain whether or not it has a part in the concomitant jaundice.

Functional obstruction explains many of the cases where symptoms of pain, fever, and jaundice recur after cholecystectomy. The disease termed idiopathic cyst of the common bile duct may also be explained by this spasm or hypertonia of the sphincter of Oddi.

The treatment of this type of jaundice varies with each case. Drainage by the Eihorn tube will usually suppress the jaundice, but not the underlying disease, and the icterus may return when drainage is stopped. Intermittent drainage over a long period of time is satisfactory in some cases. If medical treatment is unsatisfactory, surgical methods must be used to cause the bile to flow elsewhere than through the ampulla Vater. There is no danger in operating in such cases even if the jaundice is of long standing.

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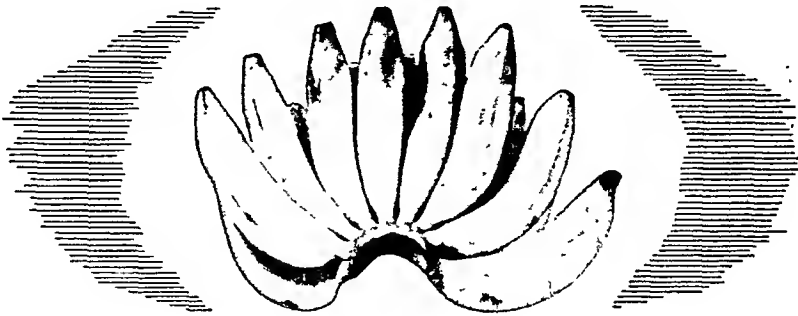
NEW YORK, N. Y.

MOSENTHAL, H. O.

Pancreatitis and Diabetes. Ann. Int. Med., XI, 1001, Dec., 1937.

As an introductory the author makes a statement that the involvement of the pancreas as a cause for diabetes is to a large extent taken for granted. He thinks that the situation is quite similar as if all pulmonary conditions, such as tuberculosis, pneumonias, etc., were classified as a disease entity characterized by expectoration and treated alike on that basis. He calls attention to the well established fact that such pathological changes in the pancreas as carcinoma, cyst, adenoma, etc., are very well established, but that the lesions found in the pancreas in cases diagnosed clinically as diabetes mellitus are not satisfactorily evaluated. In his attempt to correlate the changes in the pancreas with the manifestations characteristic of diabetes, he adjures the reader that the conclusions reached are but tentative and that further laboratory, as well as clinical data, must be had.

While diabetes is caused by an involvement of a majority of the islands of Langerhans, attention is called to the fact that a pancreatitis that results from such lesions may be permanent or transient and that it may be chronic or acute. He thinks that chronic pancreatitis that develops in elderly people as a result of arteriosclerosis and other senile changes should really be



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classified as a primary chronic pancreatitis, that this form of pancreatitis is a slowly progressive change that occurs in late middle life or old age and may be generally recognized as the essential diabetes of Naunyn and rests primarily from a causative factor at a point upon the degenerative changes that are incident to advancing years. He sharply distinguishes this form from those forms of diabetes that are found in younger people that are characterized by periods of exacerbation and remission.

Hyalinization of the islands occurs almost entirely in persons over 40 years

of age, but it may be also found in non-diabetics. Fibrosis is more frequent in older individuals and yet it is not often mentioned as a cause for diabetes. Fibrosis and hyalinization of the islands may be found in the same pancreas, in fact, the two lesions may even be combined in the same island.

When a chronic pancreatitis is the sequel of scarring, resulting from an acute pancreatitis or from pancreatic duct obstruction, it should be considered as a secondary chronic pancreatitis in contradistinction to the above chronic form which is called the primary chronic type. In the secondary

type of chronic pancreatitis the destruction of cell tissue is brought about through pancreatic calculi or external pressure or acute pancreatitis, by pancreatic cysts or by hemorrhage within the tissue of the gland. The subsequent development of the diabetes depends entirely upon the number of islands which are destroyed. If only a few are killed, clinical diagnosis does not result. The diabetes from the secondary type of chronic pancreatitis is usually mild and generally non-progressive.

Classification of Fitz, designating the varieties of acute pancreatitis as hemorrhagic, gangrenous and suppurative, is followed, though attention is invited to the thought that they should be considered as parts of the same process, namely, acute pancreatitis. Pratt is quoted as stating that these forms of acute pancreatitis "represent different stages in the same pathological process that begins with necrosis of the pancreas." Gall bladder disease, edema and hemorrhage of the pancreatic parenchyma are mentioned as causes of acute pancreatitis.

Clinical manifestations are considered under three headings and this classification holds good whether the cause be chronic or acute pancreatitis.

1. Carbohydrate metabolism. This is interfered with to a very mild degree and there is only a tendency to a very slow progress in the chronic type due to arteriosclerosis, whereas in younger individuals the interference with carbohydrate metabolism is much more marked, though it must be recognized that an acute pancreatitis may or may not be accompanied by hyperglycemia and glycosuria. Likewise it may cause the transient appearance of diabetes which will subsequently clear up.

2. Fat metabolism. While the oxidation of fat is associated with carbohydrate metabolism, yet it must be remembered that the oxidation of fat does not depend entirely upon the utilization of glucose but only that the oxidation of B-oxybutyric acid is contingent upon the carbohydrate metabolism. Other agencies determine the change of a fatty acid in a chain of 16 or 18 carbon atoms to the 4 carbon chain of B-oxybutyric acid. It is an excess of this latter fatty acid that results in diabetic acidosis.

The oxidation of fats up to the B-oxybutyric acid stage, while not influenced by the islands of Langerhans, is a pancreatic function. The evidences of a disturbed fat metabolism in the diabetic are hypercholesterinemia, lipemia, xanthoma and a fatty liver and spleen. A hypercholesterinemia may occur in a mild diabetic with a well controlled carbohydrate metabolism and without acidosis. It may be taken as an index to the degree of lipemia. There seems to be a dissociation of fat and carbohydrate metabolism in these cases. A hyperglycemia, glycosuria,



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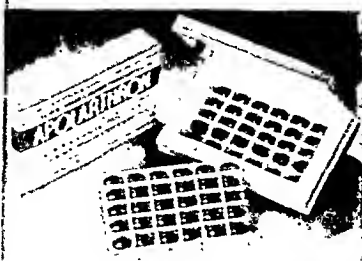
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acidosis, xanthoma and lipemia obtaining in a patient may have the blood sugar reduced to normal and the acidosis cleared up while the lipemia lags. This would appear to argue that the appearance of these products of disturbed metabolism are brought about by a suppression of a different pancreatic function. Acidosis without lipemia is common; lipemia in the absence of glycosuria likewise occurs. If the thesis of an independent control of fat and carbohydrate metabolism by the pancreas is correct, the author argues that the hormone discovered by Dragstedt and his associates, called "lipocaine" may prove the solution of a disturbance in fat metabolism through the pancreas, apart from that regulating the carbohydrate metabolism. This new substance must await clinical trial.

3. Blockage of the pancreatic ducts. This is characterized by "pancreatic stools"; they are yellow, malodorous, bulky, and there is an absence of pancreatic ferments. Evidence of carbohydrate metabolism may or may not become manifest, but whether diabetes is or is not present, the relief from the "pancreatic stools" can be secured by the administration of raw pancreas only.

The author concludes that the pancreas is the organ which, when diseased, is responsible for the disturbed carbohydrate metabolism; that chronic pancreatitis is the result of senescent processes; that acute pancreatitis, in a mild form, may be a cause of the difficult onsets of diabetes in young patients; that pancreatitis results in (a) interference with carbohydrate metabolism; (b) disturbance of the fat metabolism and (c) that an occlusion of the pancreatic ducts with lack or loss of the external secretion of the pancreas in the intestine which in turn results in "pancreatic stools."

Virgil E. Simpson, Louisville.

DRAGSTEDT, L. R.

Lipocaine, Northwest Medicine, 37: 51-56, Feb., 1938.

As a result of animal experiments the author concludes that there is present in fresh pancreas and probably in the islet tissue a specific substance, apart from insulin, which plays a role in the transport or utilization of fat. It is not present in the external secretion so it is probably an internal secretion or hormone for which the name "lipocaine" has been chosen. Without this hormone the denaccretized dog almost inevitably dies within a few months in spite of most careful dietary regulation and insulin administration, whereas with it and insulin the same animal may survive in excellent condition for several years. The substance was found to be present in the fat-free part of a 60 per cent alcohol extract of the fresh tissue.

The author calls attention to the

possibility that diabetics suffer from a lipocaine deficiency as well as an insulin deficiency, and that this manifests itself in a disturbance in fat utilization with the deposition of fat in the liver and in more chronic cases in the sub-endothelial layers of the arteries.

Hanes M. Fowler, Fort Wayne.

GUSTAFSON, EINAR G.

An Analysis of Sixty-two Cases of Primary Carcinoma of the Liver, Based on 24,400 Necropsies at Bellevue Hospital, Ann. Int. Med., XI, 882, Dec., 1937.

The autopsies from which the cases reported in this study were taken were 24,400 consecutive autopsy studies that had been made at the Bellevue Hospital in a period of thirty years from 1906 to 1936. The 62 cases that were selected for review were all primary carcinomas of the liver. 53 of the cases selected were males and 9 females. The average duration of the time when the history began until death was 3.2 months. Considered from the standpoint of cell type, it was noted that the average course of the liver cell type was 2.5 months, while that of the bile duct type was 4.1 months. From a pathological viewpoint it was found that 25 of the 39 cases of the liver cell type, or 64.1 per cent, were attended

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- *1 "Pellagra Successfully Treated With Nicotinic Acid: A Case Report." Jrl. A. M. A., 104:2654, 1935.
- 2 "Nicotinic Acid in the Treatment of Pellagra." Jrl. A. M. A., 110:222, 1936.
- 3 Jrl. A. M. A., 110:222, 1936—Editorial—"Nicotinic Acid and Pellagra."

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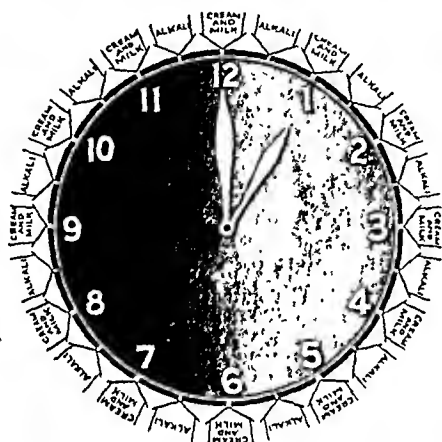
with some degree of cirrhosis, while only 3.3 per cent of the bile duct cell type showed detectable cirrhosis. In the microscopic study of tissues attention is called to the necessity of examining uninvolved tissue to exclude factors of error. For example, biliary obstruction due to tumor, encroachment on biliary ducts, will lead to fibrosis of liver tissue, yet this fibrosis is biliary in origin rather than portal. Only two cases of the series were of the dual or indeterminate type of cell structure. The study of metastases in the group brought out the following features. Solitary distinct metastases as to brain, bone, kidney, etc., were not uncommon. In 19 cases, or 30.6 per cent, even naked eye evidence of neoplastic venous thrombosis was present. In six of the 19 cases there were visceral metastases likewise visible to the naked eye. In two cases tumor thrombi were found to have travelled through the inferior vena cava to the right auricle of the heart. In several the splenic vein was thrombosed throughout its entire length. In 29 cases, or 46.8 per cent, there were no naked eye evidences of metastasis. In the remaining 33 cases the sites of metastases were numerous, more frequently in the periportal lymph nodes and the lungs, particularly the right lung. Only 3 cases of metastasis to bone were found. One of these was found in the ribs, vertebral and left orbital bone. In the other two the ribs only were involved.

Reference to the size of the liver was made and in 48 cases the liver had been weighed. The average was 2900 grams. There was very little difference in the size of the liver in the liver cell type of neoplasia and in the bile duct type. Ascites was present in 72.6 per cent and was found to be the most constant approximate in the series. The ascites was bloody in six and sero-sanguineous in seven others. An enlarged spleen was found in a majority of cases. The average was 351 grams and was slightly higher in the bile duct type of tumor. Jaundice was infrequent in neoplasia of the massive type. This was explained on the basis of biliary obstruction by pressure from tumor nodules, and in tumors of the massive type secondary nodules were infrequent.

Only seven of the whole 62 cases of the series were diagnosed clinically. One had been diagnosed as carcinoma of the stomach with metastasis to the liver. Another had been diagnosed as cirrhosis of the liver, another as carcinoma of the head of the pancreas, and another as malignancy of the liver with the primary site undetermined, and another of cardiac decompensation. In the remaining 55 no available data was found in their study to show that the possibility of primary carcinoma of the liver was even suggested.

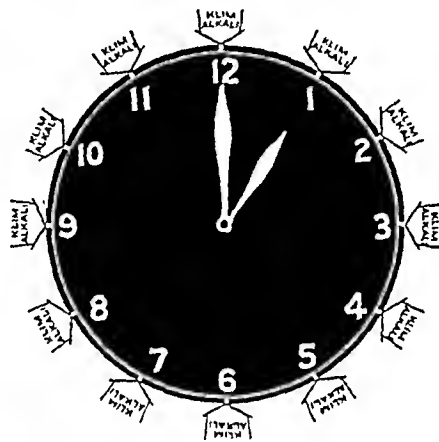
Reference is made to the criteria which Symmers in correlating his

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*Ann. Int. Med. Vol. 9, No. 2, Feb., 1936



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twenty years experience in the necropsy room and wards of Bellevue Hospital had set up. These criteria were:

- (1) A male patient over thirty-five years of age.
- (2) A large palpable tumor mass in the right lobe of the liver.
- (3) No primary tumor discoverable elsewhere.
- (4) Jaundice, usually mild.
- (5) Ascites.
- (6) An otherwise unexplained fever of mild degree.

As a consequence of this study the following conclusions were drawn:

1. Primary carcinoma of the liver occurred once in every 324 necropsies at the Bellevue Hospital in the thirty years covered by the study. This represented an incidence of 0.25 per cent on the 24,400 necropsies.
2. Primary carcinoma of the liver is a clinical and pathological entity susceptible of diagnosis during life.
3. The clinical diagnosis may be postulated with reasonable certainty on the criteria set up by Symmers.
4. Cirrhosis was found in 51.6 per cent in association with the tumor and in six cases hemochromatosis of the liver was found in conjunction with cirrhosis.
5. The bile duct type of tumor is histologically indistinguishable from the duct cell carcinoma of the pancreas.

Virgil E. Simpson, Louisville.

CASTLE, W. B., HEATH, CLARK, W., STRAUSS, MAURICE B. AND HEINLE, ROBERT W.

Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia. (From the Thorn-

dike Memorial Laboratory, Boston City Hospital and Harvard Medical School). Am. Jour. Med. Sciences, p. 618, Nov., 1937.

It is assumed "that the effective principle in the liver of the normal person is in some way formed from the interaction of food and gastric factors. The problem as to how and where in the body such a transformation occurs remains, however, quite unsolved." "Normal human gastric juice freed by absorption methods of both pepsin and rennin still contains intrinsic factor." "Administration of beef muscle and gastric juice, separately at an interval of 6 hours results in increased blood production." This the authors say "eliminates the necessity of hypotheacating an in vitro phase for the production of the activity of incubated mixtures." When the administration of beef muscle and gastric juice are separated by an interval of 12 hours or more there is a negative effect upon blood production. "Neutral mixtures of gastric juice and beef muscle are effective when administered to the achylic pernicious anemina patient. Therefore, so far as the reaction is concerned a suitable environment might be found as well after absorption within the body as before leaving the alimentary tract." The authors found that "Mixtures of beef muscle and gastric juice administered at pH 1.8 to 2.5 are ineffective." If, however, such incubated mixtures were given at pH 5 or pH 7 a positive effect on blood production appeared.

"Whether failure of the acid digest to cause increased blood production was due to the destruction of the extrinsic or intrinsic factors before effective interaction could occur or whether it was due to such acidity that interaction could not take place was the basis of further analysis." As it was found that incubation of the beef muscle and gastric juice mixture at pH 1.8 or 2.5 for 6 hours did not abolish its activity if it was brought to pH 5 or 7 before administration; if the mixture was not so neutralized it could be argued that after it was given to the patient continued in vivo incubation of the acid mixture was responsible for failure through subsequent destruction of the intrinsic factor. This question was put to test and the authors found it probable that "the negative effect of administration of incubated mixtures of beef muscle and gastric juice at an acid reaction, was not due to a prolongation of any destructive action of the acid medium on the extrinsic or intrinsic factors after administration to the patient." The writers found that "temperatures without significant destructive effect on aqueous solutions of an unpurified liver extract abolish the activity of mixtures of beef muscle and gastric juice after incubation for 2 hours at pH 7." In addition they found that "temperatures without significant destructive effect on aqueous solutions of liver extract abolish the activity of mixtures of beef muscle with normal human duodenal contents or with hog duodenal and small intestinal mucosa after incubation for 2 hours at pH 7." They further state that "the destructive effect of temperature on the mixture given these patients was not on the extrinsic factor in the beef muscle is clear. Mixtures of gastric juice with a 48 hour peptic digest of beef muscle previously boiled for 5 minutes with autoclaved, autolyzed yeast or with hog stomach mucosa which has been boiled for 2 hours, are hematopoietically effective."

Allen Jones, Buffalo.

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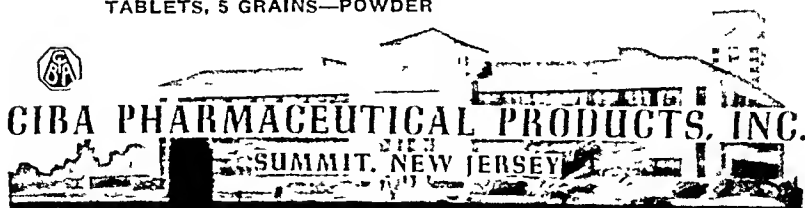
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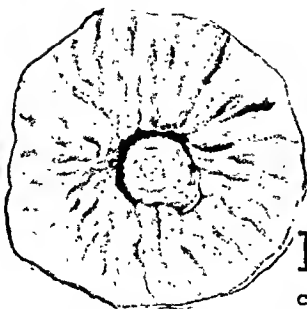
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By

JULIAN M. RUFFIN, M.D.*
DURHAM, NORTH CAROLINA

FOR many years amebic dysentery has been regarded as a tropical or subtropical disease (1). The recent epidemic in Chicago (2) tended somewhat to discredit this belief, but so firmly is its tropical nature fixed in the minds of the profession that the disastrous consequences of that outbreak may soon be forgotten, or at least, it will no longer occur to many of us who live in the temperate zone that the cause of our patients' illness may be an amebic infection.

The purpose of this communication is to emphasize the prevalence of the disease; to show how easily the diagnosis can be made; to point out the gratifying results which almost invariably follow adequate treatment; and to warn the profession of the tragedy which frequently overtakes the improperly treated or neglected patient.

Material: This report is based upon a group of 54 patients with proven amebic infection who have been studied in Duke Hospital during the past six years. The distribution according to race and sex is shown in Table I.

TABLE I

	Male		Female		Total
	White	Colored	White	Colored	
Number	41	5	6	2	54
Percentage	76	10	11	3	100

All ages were affected; the youngest patient in this group being two years, the oldest being sixty-six years of age. The distribution by decades is shown in Table II.

TABLE II

	0-9	10-19	20-29	30-39	40-49	50-59	60-69
Number	3	3	9	14	9	11	5
Percentage	5.5	5.5	17	26	17	20	9

With the exception of one patient whose infection could be traced to the Chicago epidemic, and of three patients who lived in border counties in South Carolina, all the patients in this series were residing in North Carolina at the time of onset of the disease. The distribution throughout the State is shown in Fig. 1. The duration of the disease could not be accurately

determined in some instances, but varied from a few weeks to several years and many gave a history of one or more relapses.

DIAGNOSIS

The diagnosis was established in 46 of the 54 patients by demonstrating the active, motile forms of *Endameba histolytica* in the stool or in the material obtained by proctoscopic examination. Because of the difficulty of identification and of their doubtful significance, the presence of cysts in the stool was not accepted as sufficient evidence of the disease, though indicating a carrier state. In six patients the diagnosis was made at autopsy, and in two patients with liver abscess, typical ulcers were observed by proctoscopic examination, though no amebae were demonstrated. However, the prompt subsidence of symptoms following treatment was thought to justify the diagnosis of amebic infection in these two patients.

STOOL EXAMINATION

Repeated examination of the stools was made in 44 cases. This was positive in only 24 patients (or 55%).

PROCTOSCOPIC EXAMINATION

Proctoscopic examination was performed in 35 patients. Typical punched out ulcers with normal intervening mucosa were observed in 31 of these patients (88%). In one patient with a liver abscess the mucosa was entirely normal, and in the remaining three patients the proctoscopic picture was suggestive of an extensive non-specific ulcerative colitis, yet amebae were demonstrated in smears. Smears obtained by proctoscopic examination were positive in 32 patients (91%).

BARIUM ENEMA

X-ray examination of the colon by barium enema was made in 19 cases. In 6 of these (32%), the colon was reported entirely normal. In the remaining 13 patients, the portions of the colon which were reported as exhibiting evidence of infection are shown in Table III.

TABLE III

	Cecum	Asc.	Trans.	Desc.	Sigmoid	Rectum
Number	5	5	4	9	10	5
Percentage	28	35	31	70	77	35

In no case could the diagnosis of amebic dysentery be definitely established from the X-ray findings alone.

COMPLICATIONS

Six patients in this series had liver or lung abscesses. One liver abscess was drained surgically with complete recovery. Three were treated with emetine, with

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gradual subsidence of symptoms, and were discharged as cured. In two patients the abscess ruptured into the pleural cavity and the diagnosis was made at autopsy. Neither of these received specific treatment. One other patient had a pelvic abscess, and another a generalized peritonitis from a perforated colonic ulcer. Both of these patients were moribund on admission and died shortly thereafter.

TREATMENT

There were 35 patients with frank, uncomplicated amebic dysentery who were treated intensively with carbarsone, yatren, or emetine, or combination of these three drugs, as shown in Table IV.

TABLE IV

	Carbar- sone	Yatren	Emetine	Carbar- sone and Yatren	Emetine and Yatren
No. of patients	10	8	5	11	1
No. days before subsidence of diarrhea	3-4	3-4	4-5	2-3	3-4

The doses used were: carbarsone 0.25 Gm. twice daily for ten days orally; yatren 5 Gm. in 250 c.c. of water as a retention enema daily for 7-10 days, and emetine hydrochloride 0.1 Gm. subcutaneously daily for 7-10 days.

In a great majority of these patients a marked change in their general well being was noted twenty-four to forty-eight hours after starting the treatment, and the diarrhea was checked by the third or fourth day. The best results were obtained with the use of carbarsone by mouth in combination with yatren as a retention enema. In 18 patients the appearance of the

cating disease was unaffected. Anderson, Delprat, Weeks and Reed report a similar experience (3).

RELAPSE (FOLLOW UP)

Information in regard to the condition of the patient since leaving the hospital was obtained in 22 patients. In 6 of these there had been a definite relapse which promptly subsided after another course of treatment. There was no relationship between the relapse and the drug which had been used.

DEATHS

There were seven deaths in this series, a mortality of 13%. Six of these patients came to autopsy. Two had liver abscesses which had ruptured into the pleural cavity. One had a general peritonitis from a perforated ulcer. Three had extensive involvement of the colon but had received no treatment, and the patient, on whom there was no autopsy, had a pelvic abscess.

DISCUSSION

Several points of interest are brought to light by this study. Of greatest importance is the prevalence of the disease in a state whose climate is far from tropical. That the disease is endemic and widely scattered over the state is shown by Fig. 1. Amebic dysentery is not reportable in North Carolina, consequently this group certainly represents only a fraction of the total number of patients. It is possibly of some significance that very few patients came from the western part of the state which is largely rolling or mountainous country.

The importance of proctoscopic study is shown by the fact that stool examinations were positive in only 55% of the cases, whereas, the smears taken from the ulcers were positive in 91%. The appearance of the ulcers seen on proctoscopic examination is so characteristic as to be diagnostic. Occasionally, there is extensive ulceration which is confusing and the examiner must decide between a chronic ulcerative colitis and severe amebic ulceration with secondary infection. In such cases the therapeutic test must be

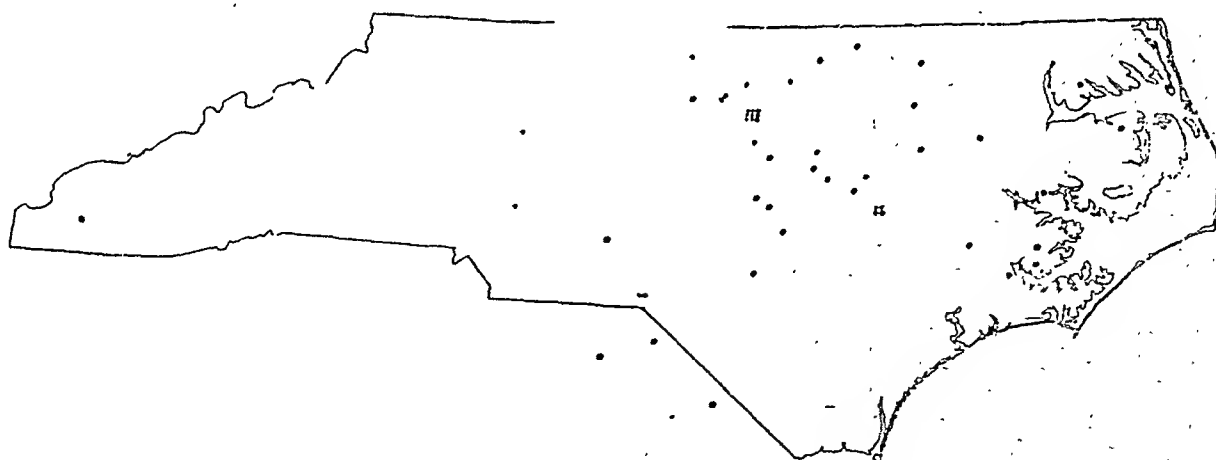


Fig. 1. Distribution of cases in amebic dysentery.

rectal mucosa was observed by proctoscopic examination after treatment. Evidence of healing was noted as early as the fifth day, and by the tenth day all traces of the ulcers usually had disappeared. In 5 patients, a mixed infection was present (ulcerative colitis in four cases, and typhoid fever in one). These patients showed very little improvement under treatment. The amebae disappeared from their stools, but the compli-

resorted to. It is a fairly safe rule that any diarrhea which fails to respond to adequate specific treatment is not due to amebic dysentery.

While it is generally accepted that the cecum is the site of predilection in amebic infection (4), in this series ulcers could be demonstrated by proctoscopic study in 31 out of 35 patients (88%); and in 5 patients coming to postmortem, ulcers were present

not only in the cecum but also in the rectum. In the sixth patient, the rectum and sigmoid were normal, the ulcers being confined to the cecum and ascending colon. X-ray studies likewise confirmed the impression that the descending colon, sigmoid and rectum were much more frequently involved than formerly had been thought.

Complications are all too frequent and usually serious if not fatal (5, 6, 7, 8, 9). In this series there were 8 patients, or 15%, with complications such as liver or lung abscess, or peritonitis from a perforation.

It is of interest to note that in three patients, the infection developed shortly after operative procedure—one after an appendectomy, one after a hernia repair, and one after prostatic resection. It is suggested

that these patients were carriers and the operation precipitated the active disease.

Finally, the gratifying results (10, 11) which almost invariably follow adequate treatment should be emphasized. Patients who have been ill for months or years are relieved of their symptoms within two to three days. In this series no deaths occurred in patients who had received adequate treatment.

CONCLUSIONS

1. Amebic dysentery is prevalent in North Carolina.
2. Diagnosis is relatively easy, if proctoscopic examination is employed.
3. Adequate treatment is highly effective.

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The Proctological Aspects of Diarrhea*

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INTRODUCTION

THE proctological significance of diarrhea is attaining increasing importance as an aid in the diagnosis of many disorders classified under the inaccurate term "colitis." In the light of our present knowledge, one is not justified in assuming that a gastro-intestinal investigation is complete unless a proctosigmoidoscopic examination has been made. This direct visual examination of the anus, rectum, and pelvic colon has no substitute, and it should be the harmonious accompaniment of the barium enema and other indirect methods of investigation. We are all, including the roentgenologist, aware of some of the inherent difficulties experienced in demonstrating some of the ulcerative and early malignant lesions of the rectum and pelvic colon and it is in this type of case that direct visual examination of the accessible portion of the bowel is clearly indicated.

All cases of diarrhea demanding or requiring thorough investigation should have a detailed history and general physical examination. Competent laboratory examination of the stools for parasites and ova, bacteriological studies of the stool and of cultures and scrapings obtained during sigmoidoscopy should be evaluated. Gastric analysis and cholecystograms may be indicated. Special hematological studies, basal metabolism and skin tests should be done when indicated.

If we are all able to completely investigate a cooperative patient and make a correct diagnosis there should be very little excuse for the existence of the food faddist, the quack, or the charlatan. Patients who sometimes consult such really belong to the clientele of the ethical internist and gastro-enterologist, and both of these physicians should consider the endoscopic visualization of the anus, rectum, and pelvic colon as a part of their diagnostic armamentarium. One should be aware that proper interpretation of findings is essential to this examination. Gentleness and ease of examination should be developed, and lest anyone is not aware of some of the dangers, they are respectfully referred to Crohn's article "Trauma Resulting from Sigmoid Manipulation" (1).

Diarrhea, as induced by some of the more common disorders, is discussed from a proctological standpoint.

ACUTE DIARRHEA

Contrary to popular opinion, the individual who conducts a proctoscopic examination upon a patient in the throes of an acute diarrhea, is neither a hero nor a fool. In the absence of an inverting type of table, it is possible to conduct such an examination in the home, hospital, or office by inverting the patient over the edge of the bed or the examining table. A pillow placed on the floor, upon which the head and elbows may be rested, can be used. Liquid stool will thus not be forced out of the instrument. I might also state that the instrument with the proximal light is handled

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with greater ease in these cases than one with the distal light. The continual soiling of the distal light, or its "window," may prevent adequate examination.

In preparation for examination, the patient is requested to take a plain water enema one to two hours before examination. It is to be noted at this time that a mistaken interpretation of "injection and inflammation of the mucosa" has often been made following the administration of a medicated enema, notably of the strong soap suds variety. Excessive purgation, especially with the saline group of cathartics and the strong vegetable compounds, may induce a low grade inflammatory change in the lower bowel. Adequate cleansing with plain water—until the return flow is clear—represents the ideal preparation for proctosigmoidoscopic examination.

In the presence of an active acute diarrhea, as previously mentioned, what should one expect to encounter upon proctological examination?

In the first place, an inflamed, reddened and eroded anal canal will confirm the patient's complaint of irritation, soreness, burning, "fever," and pain in the anus which is aggravated by stool. In general, the more active the diarrhea, the more severe the anal irritation. An acute "attack of piles," may supervene when one or more hemorrhoids may become thrombosed or extruded. The entire anal ring may be everted in severe cases, and in most cases a variable degree of edema, redness, swelling, and inflammation may be encountered. An attack of prolapsed, strangulated, thrombosed hemorrhoids is brought on as frequently by an acute diarrhea as by the passage of a hard, constipated stool. Multiple fissuring of the anus, with eroded petechial spots or larger longitudinal breaks in the mucosa of the lower rectum and the skin of the anal canal, may occur so that the simple eversion of the anus during examination produces an active oozing of fresh blood. Marked spasm of the sphincter is the rule and one may not be able to examine the patient further. Palliative measures such as Sitz baths, warm applications, warm plain water enemas, or retention enemas of warm oil may be of value in alleviating the local condition so that examination may be completed a few days later.

When seen through the proctoscope, many cases of acute diarrhea will present nothing more than an active hyperemia of the lower 1 to 2 inches of the rectum. The blood vessels are engorged and stand out in a spider-web appearance to a degree greater than seen in the normal bowel. Small web-like patches of vessels may appear like a naevus with free intermingling of arteries and veins. After several days, the bowel may become edematous, and the glistening, translucent appearance of the mucosa may give one the impression that it is greatly thickened. This increased congestive vascularity is accompanied by spots and diffuse areas of bloody oozing which occurs by diapedesis. Ulceration of the surface does not develop unless the diarrhea is prolonged, when the mucosa becomes eroded and secondary infection of the bowel wall occurs. The bowel surface is easily traumatized, and half-moon shaped abrasions may be readily produced by the end of the instrument. Swabbing the surface may be sufficient to produce bloody oozing. The amount of mucous secretion is considerable and when mixed or streaked with blood, bacterial activity may produce a mucopurulent, bloody exudate even

though the bowel surface appears intact. The lower 2 to 3 inches of the rectum are usually affected and there is no sharp line of demarcation. Inflamed bowel gradually blends with normal bowel. Involvement of the entire rectum and extension into the pelvic colon should put one on guard and further examination and studies are indicated. This is likewise the case if an inflammatory process appears in the pelvic colon and seems to progress from there towards the rectum. These temporary, inflammatory reactions of the rectal mucosa should be observed and every effort should be made at an early date to separate them from the more serious disorders, mostly of a true infectious nature.

ULCERATIVE COLITIS

The diarrhea of ulcerative colitis may have an acute, chronic, or insidious onset. The acute case may have from 6-10, or even 20 stools a day, and the patient having a chronic insidious onset may note that he is now having 4-6 stools daily whereas three to four months previously he had only 1-2 daily movements.

This is a most serious disease of the digestive tract, and it may tax the ingenuity of the internist and gastro-enterologist before the diagnosis is made. Especially is this true in the regional and segmental forms of ulcerative colitis. However, from the diagnostic angle, we should be encouraged by the fact that 90% or more of cases of ulcerative colitis have their beginning in the rectum and pelvic colon. The fact that such a high percentage of these cases can be identified by proctosigmoidoscopy and culture should encourage all who see cases of diarrhea to examine the bowel by direct visualization, so that an early diagnosis of this disease may be made. It is thus obvious that a high percentage of cases of ulcerative colitis would therefore be correctly diagnosed at an early stage if they were examined with the sigmoidoscope.

If a patient consults one during the early phase of an ulcerative colitis, he may expect to encounter the following picture during proctosigmoidoscopic examination.

The mucosa of the lower rectum may appear inflamed similar to that described previously under acute diarrhea. There may be a gradual transformation into normal mucosa within the field of vision. However, the process is often more extensive and involves the pelvic colon beyond reach of the instrument. There is no early pathognomonic appearance, and a diagnosis of ulcerative colitis cannot be made from the visual aspect alone. A positive diagnosis may be made from cultures obtained at this time. As the disease progresses, the bowel wall appears more edematous and slightly thickened. The bowel wall is less pliable, the folds of mucosa stand out more firmly than usual and when the edge of the instrument scrapes any surface, bleeding readily occurs. The mucosa gradually develops a granular, glistening appearance, and minute mucosal abscesses appear. The abscesses are rarely larger than 1 mm. in diameter and they involve the bowel in a diffuse manner with a tendency for some areas to look a little patchy, appearing as if one had given a sudden "shake of pepper" to an area of the mucosa. The disintegration of these abscesses is accompanied by a surface ulceration which may be both discrete and confluent. This is a diffuse ulcerative process. The ulcers are usually small, 1 to 4 mm. in

size, and they are irregular. Numerous small ulcers may coalesce to form a larger shallow irregular lesion. Secondary invasion by the various organisms of the digestive tract tends to increase the incidence of the large irregular ulcerations. The intervening mucosa between patchy areas of ulceration is usually inflamed, edematous, and diffused with the small submucosal abscesses. Very little normal looking mucous membrane may be seen. This irregular ulceration is considered characteristic of ulcerative colitis at this stage. Cultures taken at any time during the pre-ulcerative phase or during the ulcerative stage may reveal a multiplicity of organisms. Identification of the responsible organism, or group, presents a bacteriological problem beyond the limits of this paper. It is felt, however, that Bargen has made the most outstanding contributions to this work that have been presented within recent years, and for that reason "Ulcerative Colitis" of the Bargen type is being discussed.

This early stage of ulcerative colitis is definitely a medical problem; no single mode of therapy is applicable. A rational, symptomatic management, as in tuberculosis or cardio-renal disease, is indicated.

The disease can be followed very readily, in its progression or regression, by the use of the proctosigmoidoscope. The proctologist and the roentgenologist can usually demonstrate the extent of the disease and some index of its activity and the degree of infection may be gathered by frequent sigmoidoscopy. Beyond reach of the instrument, the course of the disease is best followed by the roentgenologist.

The chronic, recurrent type of ulcerative colitis presents a different proctosigmoidoscopic picture. As a result of the chronic infectious process many unique and bizarre findings may be observed. Areas of new and old ulcerations are interspersed with areas of healing, scarring, and contracture. Irregular, depressed, pock-marked scars may be seen between areas of shaggy, necrotic tissue protuberances and mucosal folds. The bowel appears as a semi-rigid tube and the mucosal folds do not roll back and away from the instrument as it is being introduced, nor do they show much tendency to roll and "pout" into the lumen of the instrument. When the lumen is contracted, there occurs resistance to the passage of the instrument and bleeding follows as the granular surface is touched. Exudate and sloughing, and irregular patchy areas, may be seen. The ulcerated bowel rarely presents any areas of normal mucosa, and in contrast to the small miliary ulcerations in the early case, the ulcerations are larger. They may attain the size of 1 to 2 cm., due to secondary infection and loss of bowel resistance. The discrete, serpiginous, and confluent ulcerations of this chronic process may give one the impression of looking at a relief map with its geographical irregularities. The term "geographical ulcerations" might well be applied to many of these cases. This chronic phase of ulcerative colitis may present some of the complications peculiar to this disease. We mention particularly stenosis and a tendency to polypoid degeneration with or without malignant changes. Hemorrhage and ulcerative perforation of the bowel are omitted from a proctologic standpoint, although one should use extreme caution in manipulating an instrument in the scarred, contracted bowel, lest accidental perforation occur.

The stenosis of the bowel develops as an irregular,

diffuse process with very little tendency to the formation of the "diaphragmatic" type of stricture. The long, irregular, tubular narrowing is the rule when stenosis does develop. The degree of stenosis is often indicative of the duration and the severity of the disease.

Cases of virulent infection or of long standing are prone to develop a polypoid degeneration of the mucosa. The mucosa between healed and unhealed areas has a tendency to pile up so that rough, irregular fragments may be seen. In other areas, the mucosa may infold upon itself and produce an actual cystic inclusion of cells, secreting mucus, which appears as a smooth, pinched-up mucosal bud which is commonly dark red in color. One has the impression of looking into an inflamed, moth-eaten tube, irregularly studded with small polyps. The bowel which shows any evidence of polypoid degeneration should be carefully watched, and any suspicious areas within reach of the proctosigmoidoscope should be subjected to biopsy. A considerable number of patients affected with polypoid degeneration exhibit malignant change, provided the patients live long enough to have such transition take place.

It is not the purpose of this paper to discuss any of the characteristics of the diarrhea or the stools in these cases. The proctoscopic findings are presented as an aid to the etiologic diagnosis of a diarrhea. One should be able to make a diagnosis of ulcerative colitis from the visual appearance of the bowel. Stool cultures from material obtained through the instrument, direct smear examination of the scrapings and the biopsy examination of tissue bits are indicated as an aid in establishing the diagnosis.

AMEBIASIS

Amebiasis should be considered as a disease entity which may have as one of its manifestations an amebic colitis accompanied by diarrhea. The colonic manifestations of amebiasis may vary from the acute fulminating type of ulcerative colitis to those atypical clinical conditions known as "irritable colon," "spastic colitis," "mucous colitis," etc.

The differentiation of amebic colitis from types of infectious colitis often presents considerable difficulty. I wish to emphasize that the ultimate diagnosis of amebiasis rests upon the identification of the pathogenic ameba or their cysts in stools, or scrapings obtained at proctoscopic examination. In the presence of an outbreak of dysentery in a community one may make a presumptive diagnosis of amebiasis. This should be confirmed by the visual findings of bowel ulcers which will be described later; however, the final decision depends wholly upon isolation of the pathogenic organism or its cysts. Cultural and serological methods of diagnosis are beyond the limits of this paper.

Proctosigmoidoscopic examination in a suspected case of amebic dysentery will ordinarily be positive in the early case, although it is less frequently positive than it is in ulcerative colitis. The fresh case with active diarrhea is more liable to show ulcerative lesions than the older case. Hinman and Kampmier (6), in a study of four hundred cases of active amebic dysentery in New Orleans, reported visible ulcers in 261 cases out of 299 proctoscopic examinations. This high incidence of visible ulcers is not seen in the older

cases. The ulcerative lesions of amebiasis may occur anywhere in the colon; their absence in the lower visible segment does not rule out this disease. The early inflammatory stage of amebic colitis cannot be differentiated from any other active lesion. When ulcerations develop, they are about 3 to 5 mm. in diameter. They are superficial, usually discrete and they may be scattered in patches about the mucosa. They are larger than the ulcers of ulcerative colitis. The superficial ulcer has irregular, sharply defined, ragged, and undermined edges surrounded by a halo of inflammatory change. As the ulcer deepens, the inflammatory reaction creates a nodular projection of the mucosa, the center of which is occupied by the ulcer. Its surface is covered with a thick purulent exudate mingled with necrotic material and mucus and vegetative forms of the ameba. This "umbilicated" ulcer is considered pathognomonic for amebiasis. The intervening mucosa is slightly injected and hyperemic, but it will ordinarily appear more normal than in ulcerative colitis. Miliary abscesses as seen in ulcerative colitis, are not present unless a burrowing, secondary infectious process develops in the area of amebic ulceration. This may appear as a "satellite" formation around the edge of an individual ulcer. Direct examination of the material swabbed from these ulcers will ordinarily reveal the vegetative form of the ameba.

The older cases of amebiasis with the larger, confluent ulcerations, that have developed as a result of secondary infection cannot be visually differentiated, with any degree of certainty, from the older case of infectious ulcerative colitis. Here one notes the same type of secondarily infected, large, irregular, serpigenous, and "geographical" ulceration. Coalescence of ulcers may produce a large, denuded surface, and, in cases of any duration, the infiltration of the submucosa and the remainder of the bowel wall tends to produce rigidity. Firm, irregular stricture is unusual unless an inflammatory and proliferative lesion—an amebic granuloma—has developed. Such is uncommon; only by biopsy, "therapeutic" test, or clinical course may it be differentiated from malignancy. Stenosis of the bowel of the diffuse type may occur, and here the long "moth-eaten," ulcerating tube may be observed.

Ulceration and fissure formation may occur about the anus and an amebic infestation of the buttocks may be, indeed, a disabling condition.

While the proctoscopic picture of a few, discrete umbilicated ulcerations is regarded as pathognomonic by some clinicians of amebic colitis, one must remember that the lesions although they exist may not always be visible at sigmoidoscopy. Experienced proctologists may make the diagnosis of amebiasis from the endoscopic findings alone, but however, experienced the clinician may be, the final proof still rests upon the identification of the pathogenic ameba. When scrapings from the mucosa do not exhibit the organism, in an instance where the diagnosis of amebiasis is highly probable, stools secured following free catharsis by epsom salts usually reveals both the vegetative or encysted ameba if such stools are properly collected and examined by an experienced laboratorian.

One should be mindful of the simultaneous presence of non-amebic ulcerative colitis in instances of amebiasis, hence one should take the routine scrapings,

cultures, smears, etc., so that the material can be studied with respect to the organisms of Bargen, Flexner, Welch, Sonne, etc.

MALIGNANCY

Diarrhea has a variable incidence as an early sign of malignancy of the rectum and pelvic colon. However, if one is to consider an alteration in the stool habits of the individual together with the inception of alternate periods of diarrhea and constipation as a new experience for the patient, he has suggestive information respecting bowel irritation and obstruction. When the lesion causing such change in stool habits is located in the rectum or pelvic colon, it is frequently malignant. Our statistics show that from 10 to 25 per cent of patients who have terminal colon lesions of a malignant kind, exhibit diarrhea as an early symptom. Further, there has been prolonged treatment carried out for dysentery or diarrhea without even a digital examination having been performed; in some instances, the patients themselves, have asked the physician to examine the rectum. Blood in the stool, either with or without diarrhea, may be encountered in 80 to 90 per cent of these cases. Needless to say, many patients were considered as having only hemorrhoids. Even though there has been much publicity in respect to the frequency with which simple, bleeding "piles" in the middle aged are actually instances of malignancy, the profession still neglects routine digital examination of the rectum. In the histories of our patients with low colon malignancy, constipation was recorded in from 50 to 75 per cent.

Diarrhea, constipation, alternate diarrhea and constipation, and blood in the stool, raise questions whose answers will be dependent upon the type of individual we are investigating. The recognition of these symptoms will vary as is attested by the patient who states that he does not have diarrhea, but that he goes to stool 6-8 times a day "to get rid of a little wind and mucus." If we asked this patient if he had frequent movements, the answer would be "Yes," but if we ask him if he had diarrhea, the answer would be "No."

We should consider the symptoms alone of anorectal disease as untrustworthy and proceed accordingly. The symptom diarrhea, with or without bloody stool, is unreliable except as it directs attention to the fact that both a digital and proctosigmoidoscopic examination of the rectum and pelvic colon is indicated. In respect to roentgenological evidence of malignancy, the following comment by Jones (7) seems pertinent—"As the average roentgenologist can make a correct diagnosis of carcinoma of the rectum in only 40 per cent of cases, it is evident that it is hardly reasonable to depend upon such a method when proper digital and proctoscopic examination will give the diagnosis in 100 per cent of cases." This statement is true in the experience of all who have occasion to deal with carcinoma of the rectum.

In discussing rectal malignancy, it is felt that the large, proliferating, fungating, necrotic cauliflower mass does not demand description here. When proven by biopsy, the diagnosis is settled. The small, discrete, ulcerative lesion should be considered malignant until proven otherwise. These irregular, ulcerative, excavating lesions nearly always appear as a single crater with slightly raised, indurated, irregular borders. The immediate surrounding area may be slightly inflamed, but the adjacent and remaining mucosa is normal.

Lesions less than 1 cm. in diameter usually do not show any fixation. This small ulcerative process must be differentiated from a solitary amebic ulcer, a tuberculous lesion, and the rare and unusual ulceration of a diverticulitis. Biopsy is indicated; but we still must not overlook the presence of an amebiasis in the presence of a malignancy.

A solitary, adenomatous, proliferating mass, with or without ulceration should be given the same consideration as a solitary ulcerative lesion. Likewise the small, flat, slightly elevated, rough plaque without a pedicle, ulceration, or necrosis demands biopsy.

The scirrhus type of malignancy which may be located in the pelvic colon is apt to present some diagnostic difficulty. In passing the proctosigmoidoscope, one may encounter an abrupt stenosis of the bowel. Similarly a particularly resistant angulation of the bowel may be met even in the absence of pathology. Here it is important to prove whether or not the lumen is patent and to know, if possible, the calibre of the lumen. We should know if the diameter of the lumen is abnormal, and this calls for a knowledge of what variation there may be from normal. It is absolutely necessary to know why the instrument cannot be introduced its full length. These scirrhus lesions present a fairly sudden, uniform stenotic process. Their mucosal surface may exhibit a proliferating lesion, but more commonly there is a diffuse, sharply localized inflammation and ulceration accompanied by a firm unyielding stenosis of the bowel. There are times when one cannot see anything as the bowel mucosa folds in ahead of the instrument just as one approaches the area of stenosis. At times, by cautious air inflation, the folds may be obliterated and the lesion seen. In the absence of visible pathology biopsy is uncalled for. The X-ray films may reveal the typical "napkin-ring" deformity.

A word regarding the value of proctoscopy and biopsy in rectal malignancy.

Even the clinician of experience has been deceived by the tuberculous, amebic, luetic, and other specific and non-specific granulomatous lesions of the rectum and pelvic colon. The inflammatory, stenotic mass associated with diverticulitis may produce a picture resembling malignancy; many times, it is not until the pathological specimen is studied microscopically that the differentiation between malignancy and inflammation is possible.

Biopsy should be considered indispensable to the routine proctoscopic examination for malignancy. One specimen, properly secured, should be sufficient but additional specimens should be obtained when there is doubt. Biopsy should differentiate the granulomas and inflammatory masses from malignancy. An index of their malignant activity may be obtained by histopathological study. The lesion whose index shows it to be highly malignant requires prompt, radical treatment. Broders' classification and grading of malignancy, when properly interpreted and evaluated, is of considerable assistance in these cases.

Proctoscopy should determine the site, gross physical characteristics and amount of local fixation of malignant or other lesions. The degree of fixation may be estimated by cautiously manipulating the end of the instrument if the lesion is beyond reach of the index finger. The degree of obstruction may be accurately determined through the proctosigmoidoscope and, in properly selected cases, the passage of an irrigating

catheter through and above the lesion, may be of some value in facilitating "decompression" by permitting the passage of gas and bowel contents.

TUBERCULOSIS

In the vast majority of instances, the development of a tuberculous dysentery is secondary to tuberculous foci elsewhere in the body. The clinical picture of an alimentary tuberculosis should be substantiated by fluoroscopic and roentgenological evidence, and when possible, by proctoscopic examination. One should remember that the finding of tubercle bacilli in the stool is not diagnostic of alimentary tuberculosis. Such bacilli may have been swallowed from a lung focus. However, if there is an ulcerative or (rarely) a hyperplastic lesion in the rectum or pelvic colon, biopsy will be of some value in determining whether or not it is tuberculous.

The primary lesion or tubercle is rarely seen during proctoscopy as these patients are usually not investigated instrumentally until an active dysentery has developed. When a tuberculous ulcerative process of the rectum and pelvic colon is encountered, one may expect to find anything from a single ulcer to a multiple, irregular lesion. The ulcers are of various shapes and sizes; they do not tend to follow any axis of the bowel, as has been noted when the ileum is involved. The ulcers are ragged, irregular, and not sharply defined. They vary in size from 2 mm. to many centimeters, and the large ulcerations may be the result of coalescence of several adjacent ulcers. The base of the ulcer is rough and irregular and it may be covered by a purulent, necrotic material. This dirty, grey, tenacious slough is very difficult to dislodge. These lesions progress slowly along their periphery; the mucosa immediately around the edge of the ulcer is slightly inflamed. The intervening mucosa may be clean. These lesions do not tend to produce so great an inflammatory change accompanied by stenosis, stricture, and granulomatous formation as do some of the other granulomatous affections.

Smears for staining and material for culture should be secured. Biopsy and histopathological study are indicated inasmuch as many of the granulomatous lesions have bizarre forms and their etiology can be determined only by expert histologic study.

BACILLARY DYSENTERY

In discussing bacillary dysentery, one should remember that the acute phase of bacillary dysentery may present findings in the rectum and sigmoid; findings which are no more distinctive than those which occur in any disturbance where acute diarrhea is a symptom. This is due to the fact that the diarrhea of an acute bacillary dysentery has often subsided within 10 days to 2 weeks. The more intense and severe lesions of acute bacillary dysentery go beyond the stage of hyperemia, bloody oozing, and edema. A diffuse inflammatory process of the mucosa and submucosa presents a cherry-red appearance with free oozing of fresh blood. The picture resembles that which has been described as a "hemorrhagic proctitis." The spongy-red, bloody surface of the bowel soon exhibits a diffuse superficial ulceration of the mucosa. The ulcers are small, 2 to 3 mm. in diameter; they are superficial; they tend to be discrete; their edges are smooth; and they involve only the mucosa. This may

be observed during the early days (5 to 10) of the disease, and the lesions may heal rapidly thereafter. This affection must be distinguished from that of acute diarrhea, and during the acute stage, stool cultures are indicated. Amebiasis, ulcerative colitis, and other infectious dysenteries require consideration, although the diffuse, severe, hemorrhagic appearance of the bowel in bacillary dysentery is seldom encountered in other conditions. A positive stool culture adequately differentiating the causative organism may be obtained during the early stages of the disease. As the ailment passes into the chronic phase, isolation of the specific organisms is almost impossible.

The patient who has developed a chronic bacillary dysentery is very commonly a diagnostic problem. The physician, internist, and gastro-enterologist who suspect this condition in some of their intractable cases of diarrhea and "colitis" may be greatly surprised when they perform agglutination tests on these patients. The recent work of Felsen (4, 5) has brought this disease to our attention rather forcefully, and his work appears to give additional and new value to the well-known ideas of Hurst.

The proctoscopic findings in cases of chronic, bacillary dysentery can rarely be distinguished from those of ulcerative colitis, hence, routinely one should test the blood serums of these patients by the approved methods of agglutination. The reader is referred to the proctoscopic description of the chronic phase of ulcerative colitis. It should be kept in mind that during the chronic phase of bacillary dysentery, the culture obtained by sigmoidoscopy will usually be negative for the various strains of *B. Dysenteriae*; whereas the culture for chronic ulcerative colitis, of the Bargen type, the organism is more readily found.

The segmental forms of bacillary dysentery are commonly and easily confused with ulcerative colitis, tuberculosis and regional ileitis as described by Crohn (2).

POLYPOSIS

Among the earliest symptoms presented by patients affected with disseminated polyposis of the colon, are the various types of diarrhea accompanied by griping and cramp-like pains of the lower abdomen. The diarrhea associated with polyposis may be intermittent, but the active period of the affection is usually accompanied by diarrhea to a degree that the patient experiences 10 to 20 stools daily. An occasional case begins with a bloody diarrhea, but usually the patient will recall that he has recently experienced stools containing considerable mucus and that this has been followed by the present bloody diarrhea. Until blood appears in the stools, most of the patients do not consult a physician. Especially is this true when patients consider that the blood is from "piles." Disseminated polyposis of the colon should be given consideration in cases of bloody diarrhea, and efforts should be made to determine the type of lesion which is present.

We are interested in two rather distinct types of polyposis, namely: 1. the hereditary or familial type; and 2. the acquired or inflammatory type.

The hereditary or familial type of polyposis as discussed by Erdmann and Morris (3), Wesson and Bargen (11), Yeomans (12), Soper (10), Mayo and Wakefield (8), and McKenney (9), usually appears in patients younger than 30-40 years of age. The family history is important. The patient should be questioned

as to whether a similar condition has been experienced by his mother, father, brothers, or sisters, or other close blood relatives, as has been suggested by McKenney (9). This type of colonic polyposis might well be named "familial intestinal adenomatosis," inasmuch as these lesions are true adenomata. The diffuse disseminated lesion, which involves the entire bowel from the anus to the ileocecal valve is the usual type encountered, although a patchy or segmental distribution is not unknown. Roentgen studies, especially with the air contrast enema technique, will demonstrate the extent of the lesion. Carcinomatous change may be identified by roentgenograms in many cases, but when the lesions are accessible by proctoscopy, tissue should be obtained by biopsy.

As the majority of these lesions extend from the anus to the cecum, a digital and proctosigmoidoscopic examination will usually demonstrate a very distinctive picture. The early case, without marked inflammation and induration, will feel soft and pliable with an occasional wart-like nodule being felt on the mucosa. One may palpate, singly or in patches, small pea sized growths arising from the mucosa. When inflammation has ensued the bowel wall becomes indurated and firmer, and one has conveyed to the examining finger a "cauliflower-like" feel. However, the large proliferative cauliflower mass is absent. The entire bowel wall in all of its circumference is roughened. Inasmuch as the polyps vary from 2-3 mm. to 1 cm. or more in diameter, one detects these tumor masses in size varying from that of a pinhead to a grape or walnut. Scattered over this roughened surface, a few large pedunculated growths may be felt to move freely to and fro by the examining finger. Proctosigmoidoscopic examination will reveal that the mucous membrane is diffusely studded with these growths whose form, size, and appearance will vary. Usually the bowel is injected and shows some evidence of inflammation so that one may observe small nodular "bumps" on the mucosa that stand out in relief as pale spots between smooth areas. Finger-like projections and lesions with relatively long pedicles may be interspersed between areas of smoother mucosa. As the condition progresses, infection, inflammation, and ulceration follow. Degenerative changes and malignant transformation accompany this condition, so that the old secondarily infected, ulcerated, and degenerated lesions are dark hemorrhagic red. Some of the larger polypi may slough off leaving a granulating ulcer at the base. Continued oozing of blood results in a marked anemia.

There is a definite feeling among many members of the medical profession that the majority of these cases of disseminated polyposis of the colon will undergo malignant change if the patient lives long enough. There is increasing evidence to substantiate this opinion if the lesion is identified as being of the "familial" type. For this reason, patients should be subjected to frequent roentgenological studies so that the nature and the extent of the ailment may be recognized. If malignant change appears, such radical therapy as is technically possible should be instituted in the hands of a competent surgeon.

The second type of disseminated polyposis of the colon has been designated by Erdmann and Morris as the acquired type. Bargen and Wesson have called it "post-inflammatory polyposis." Both groups agree

that the familial type differs from the acquired type. It should be emphasized that the acquired or inflammatory type of polyposis is not a true adenomatous disease. It is, in reality, a "pseudopolyp" formation. Such cases are derived from the long standing effects of ulcerative colitis, amebiasis, bacillary dysentery, bilharziasis, et cetera, in which buds and polypoid excrecences or "pseudopolyps" have developed. In this type of polyposis, the colon presents a moth-eaten ulcerated tube irregularly studded with polyps. More ulceration is present than in the former type and very little evidence of normal mucosa is apt to be seen. This is definitely a more "ragged" process, appearing as a chronic ulcerative colitis in which there is a tendency to form inflammatory buds of tissue. This is a secondary inflammatory change of the bowel associated with the infectious dysenteries; it is not a true adenomatosis.

It is suggested that the former "familial polyposis" be considered a true adenomatosis coli and that it be designated by the term "Familial Intestinal Adenomatosis," and that the name be further qualified by the location; cecal, transverse colon, pelvic colon, rectum; and by the changes present; i.e. inflammatory, degenerative, malignant, etc. Such nomenclature would indicate the status of the adenomatous process in any case at any given time.

The second type of disseminated polyposis could be well designated as "Acquired Inflammatory Polyposis."

ADENOMA

The diagnosis of a single adenoma of the rectum and pelvic colon is as important as the diagnosis of malignancy, for it has been repeatedly indicated, and proven, that many cases of solitary adenoma become malignant. Adenoma should therefore be considered as the precursor of malignancy and appropriate treatment instituted.

The first intimation of a rectal adenoma which a patient may experience is a sudden, profuse, and often alarming hemorrhage. Close questioning may reveal that there has occurred an intermittent passage of mucoid stools previously. Diarrhea is not ordinarily a prominent symptom noted by the observant patient, although the passage of mucus may be observed. In children when an adenoma is located close to the anal outlet, there may be obstipation, straining, bleeding, and the appearance of a grape-like tumor mass at the anal orifice.

The majority of single adenoma of the colon occur in the rectum and pelvic segments of the colon; therefore, they are palpable or visible to digital and proctosigmoidoscopic examination. Digital examination should determine the size, location, fixation, and induration of the lesion. Visualization of the adenoma should determine the size of the lesion, the character of its attachment and the presence of ulceration or marked proliferation. These lesions will vary in size from 3-4 mm. to many cms. in diameter. They may be smooth and shiny or rough and warty. The adenoma with the definite, small, soft pedicle without surface ulceration or proliferation, may be considered as benign although biopsy is indicated. The flat, button-like lesion is more apt to be malignant than is the long grape-like tumor. The large adenoma having a rough, irregular, cauliflower-like surface, without ulcerative spots or areas of marked proliferation, should be considered malignant until proven other-

wise. Biopsy of tissue from several portions of the lesion and its pedicle should be performed. The appearance of ulceration or proliferation on any of these lesions should be regarded as evidence of malignant change until proven otherwise.

These lesions require little visual description as their appearance is characteristic. More than one adenoma may be present, and the clinician is urged to make his proctosigmoidoscopic examination complete by inspecting the entire bowel within reach of the instrument. Roentgen study of the colon may be required before one may say that the affection is, or is not, localized to the visible portion of the bowel. In regard to adenoma and polyps, barium enema followed by the air contrast technique for demonstrating the mucosal patterns is of utmost value.

SUMMARY

This communication attempts to present the proctological significance of diarrhea, or alteration in stool habitus, from the standpoint of diagnosis by direct visual inspection of the bowel mucosa. It is hoped that the general practitioner, the internist, the gastroenterologist, and others will recognize that the judicious use of the proctosigmoidoscope should be part of their diagnostic procedures. Endoscopic examination of the anus, rectum and pelvic colon permits direct visualization of the terminal gut; there is no substitute for it. As with other investigative procedures, it is not always possible to arrive at a final diagnosis during the first examination; particularly if attempt is made to recognize pathology when the bowel has not been thoroughly emptied of all forms of residue. One cannot too severely condemn efforts at diagnosis made when the patient has not been properly prepared, or when the examiner does not completely and thoroughly inspect all of the mucosa within reach of the instrument. Stool examination should be augmented by direct smear and culture from the mucosal surface. Scraping should be examined grossly and microscopically more frequently than is the custom. Biopsy is indicated more commonly than is practiced. The presence of more than one disease, i.e. amebiasis complicating malignancy, should be kept in mind in the obscure and unusual case. The term "colitis" will mean something if we can demonstrate the cause which is truly producing inflammation of the bowel. Only in such events is it possible to have exhibited specific therapy for specific disease processes. Roentgenological investigation should be the harmonious accompaniment to the special diagnostic procedures common to the trained proctologist.

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The Importance of Recognizing Contracted Anus

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THE term "contracted anus" as used in this report designates a condition characterized by an inelastic, fibrous stricture of the anus, including the subcutaneous and muscular components, due to infection which gains entrance to the tissues through the anal crypts. Other pathologic conditions, such as anal fissure, anal fistula, hemorrhoids, hypertrophied papillae, and so forth, may occur conjointly with this disorder, but it should be understood that instead of causing contracted anus, they occur as a result of the infection which produces it.

One hundred consecutive cases of contracted anus in which patients were operated on at The Mayo Clinic are the subject of the following remarks. Only cases which presented this disorder without significant complications are considered in this series. Cases of contracted anus in association with anal fissure, fistula, hemorrhoids, and other pathologic disorders of the anus and lower portion of the rectum are not included in the report, nor are those in which contractural deformities resulted from previous rectal operations. In this series, however, are included those cases in which there were external tags, hypertrophied papillae, and small, internal hemorrhoids which occurred concomitantly with the process which was responsible for contracted anus.

One hundred years ago Herbert Mayo wrote of "cases in which spasm of the sphincter produces long-continued and most serious suffering; in which the anus becomes permanently contracted and hardened, constituting therefore a permanent stricture, and generally combining both permanent and spasmodic contraction." Miles recognized this condition of the anus; he called it a "pecten band" and regarded it as a distinctly pathologic condition resulting from fibrosis of the "submucosa" following long-continued passive congestion in the area associated with internal hemorrhoids. According to Miles, another cause of "pecten band" is passive congestion due to pressure on the veins of the rectum, this pressure occurring in constipated persons with a rectum habitually loaded with feces. Abel reiterated Miles' theory of origin, in a recent paper, and added the conception that long-continued spasm of either sphincter of the anus will cause passive congestion and subsequent deposit of fibrous tissue in the submucosa, forming a pecten band.

Zorraquin called the condition "myositis sphinctera." It is caused, he said, by slight infections of the "anal or rectal mucosa" which later impregnate the external sphincter and produce scars. In other cases the process may be less extensive and involve only the mucosa and submucosa with accompanying hypertrophied papillae and skin tags.

Rieder and Muller believed contracted anus to be due to an inability of the internal sphincter to open. Inflammation of the rectal wall, in their opinion, interferes with conduction in the fibers of the "pelvic nerve" located there. As the function of the "pelvic nerve" is to open the internal sphincter, this opening cannot be accomplished and the sphincter remains in a contracted position. They did not regard this contraction as a state of spasticity; instead they considered the opening of the sphincter to be the active phase and the contracted position the resting phase of the muscle.

Carnett recognized a chronic, undue spasticity of the external sphincter as a cause of constipation. He stated that, "in many cases, however, no irritative lesion can be found to account for the sphincterismus."

Hill and Hayden found their explanation for anal contraction in embryologic maldevelopment. They were of the opinion that mesoblastic connective tissue persisting between the hindgut and proctodeum caused in severe cases an imperforate anus, in milder cases an anal stenosis. We found in the records for the three years studied, one case, that of a child three months old, which exemplified this condition.

We agree with Zorraquin that anal contraction can exist as a fibrous deposit beneath the lining membrane of the anal canal or as a fibrosed external sphincter. It is possible that the fibrous band described as the pecten band may exist, but we have not been impressed with any instance in which this condition occurred independently of similar involvement of the sphincteric muscles surrounding the anus. It is possible that the deposit of fibrous tissue within the substance of the sphincter may occur to such a minimal degree that the pecten band appears to occur alone; but that this fibrosis could actually be limited to the subcutaneous tissues of the anus, to the exclusion of any of the adjacent tissues, seems highly improbable. In most of the cases of contracted anus which we have observed, in addition to the fibrous band the anal sphincters, or a portion of them at least, are found to be scarred and unyielding.

DIAGNOSIS

Contracted anus is suggested when a patient complains of inability to evacuate the rectum. Most of these individuals are loath to admit that they are constipated and prefer to dwell on the fact that there is a "stoppage" at the outlet of the rectum which interferes with the expulsion of the rectal content. They complain that even when they are able to defecate they are left with a sense of incompleteness and the stools are of small caliber. There is usually a sense of fullness in the rectum and the patient is troubled with a frequent desire to defecate. He has usually made use of a large portion of the innumerable laxatives and

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cathartics, all of which ultimately lose their effect and leave him in a worse dilemma than that in which he found himself previously.

The diagnosis can easily be made. On examination it will be found that the anus is contracted. It is impossible to separate the anal margins so that the first portion of the anal canal can be visualized, as may be done in normal individuals. When an attempt is made to perform digital examination, a sensation as if the finger is being pressed into the lumen of an unyielding, bony ring is imparted. Often the caliber of the ring is so small as barely to admit the tip of the finger. A significant sign is obtained when, either by pressing the finger tip against the anal margin, or when it is possible to insert the finger within the anal canal, any pressure which moves the anus will move the tissues adjacent to it so that the whole perineum also appears to move. This indicates that the contraction is not limited to the lining membrane of the anus, because in such a case the thin tube-like stricture will slide in and out of the muscular circle without moving the adjacent parts. Usually there will be accompanying pathologic changes, although it is possible for contracted anus to exist with no evidence of gross disease in the anus or about its margins. Only nine of the 100 cases studied in this series failed to show some other pathologic change. Infection of the anal crypts, that common denominator of such a great part of benign anorectal disease, is the cause of contracted anus. Internal hemorrhoids, which Miles believed to be the causative factors, spring from this same infective process that causes the fibrosis of contracted anus.

ANALYSIS OF CASES

In 27 per cent of our cases contracted anus was found with associated internal hemorrhoids, but hypertrophied papillae were also present as another evidence of the infection that caused the disorder. Internal hemorrhoids, it is true, were most commonly associated, being present in 45 per cent of the cases. Frequently hypertrophied papillae, external skin tags, or anal scars were also present in cases in which internal hemorrhoids were present, which is additional evidence that infection is a common root of all.

Eighty-four per cent of our patients were women. The severest type of constipation was present in eighty cases. A number of patients found it necessary to make pressure on the perineum as an aid in expelling the stool. Thirty-four per cent of the patients were in the age decade from forty to forty-nine years, which was more than twice the number in any other decade.

A striking fact was that 56 per cent of the patients had in addition been diagnosed as having nervous exhaustion, which diagnosis is not applied indiscriminately to individuals of a nervous type. It is applied only to patients who exhibit to an advanced degree an irritable weakness syndrome characterized by a multiplicity of complaints without positive physical findings.

TREATMENT

It is necessary in cases of contracted anus to enlarge the anorectal outlet, and inasmuch as the deposit of fibrous tissue occurs both in the subcutaneous tissues of the anus and diffusely in the anal musculature, simple incision of the so-called pecten band is insufficient. It is necessary to overcome the contractual influence of the fibrous deposits by stretching, and this

procedure should be carried out in the most careful and intelligent manner. The operation cannot be performed without anesthesia, and at the clinic we have employed sacral anesthesia for this purpose; by this method the effect of muscular spasm is entirely eliminated and usually any resistance which must be overcome is due to fibrous development.

Following the customary preparatory procedures, consisting of irrigations to empty the lower part of the rectum and the application of tincture of metaphen to the anal and perianal tissues, the rectal outlet is dilated in the following manner: The index finger of one hand is inserted through the anal canal, using whatever force is necessary to overcome any constricting influence. While this finger is held in place, the index finger of the other hand is forced slowly in beside the first until the tips of both fingers are well within the lower rectum. Further stretching is then accomplished by slowly but firmly flexing both fingers at the first and second joints. This maneuver draws the anus up higher on the third phalanges of the fingers where the diameter is greater. Next, the two index fingers are withdrawn and the index and middle finger of one hand are inserted, after which the index finger of the other hand is again forced in beside them and the maneuver is completed, as in the former instance, by flexing all three fingers. The amount of dilatation afforded in this manner will usually suffice; if it is considered insufficient, both fingers of both hands can be inserted and flexed as described. The most valuable feature of such dilatation is that the maneuver is likely to proceed slowly, and in that way the surgeon avoids the complications which often occur as a result of the usually hasty method of stretching the anus.

If there are any accompanying pathologic deformities, such as hypertrophied papillae, skin tags, and so forth, these should, of course, be excised after dilatation has been completed. The postoperative management of such a patient is of extreme importance, and if this program is carried out properly it will prevent those unfortunate recurrences which sometimes follow this method of treatment.

Each day after the bowels have acted, the rectum is cleansed by an irrigation which consists of plain water at 110° F. which is given through a small, soft rubber catheter well lubricated with a water-soluble non-irritant lubricant. Only 2 to 3 inches of the catheter are inserted into the rectum. The patient is cared for each day until the wound produced by dilatation or removal of papillae, tags, and so forth is entirely healed, or until it is in such condition that it will need no other care than that which can be carried out by the patient unassisted. Each day following the evacuation of the bowel and the irrigation, the anal canal and the wound are cleansed by irrigation with witch hazel. This is accomplished with an ordinary 20 c.c. syringe, a connecting rubber tube and a perforated irrigating tip. Many solutions other than witch hazel may be used as for example, an aqueous solution of metaphen (1:500), a saturated solution of boric acid, dilute potassium permanganate solution, and so forth. If the wound is sensitive, it is comforting to dust into it a generous amount of parathesin or anesthesin (ethyl aminobenzoate). Finally a piece of cotton of suitable size is lightly tucked into the orifice of the anus or into the margins of the wound.

A full-residue diet supplemented by agar is given

immediately after operation in order to provide bulk in the stools. No mineral oil or cathartics are given.

COMMENT

While contracted anus does not occur in a great number of cases of constipation, its diagnosis offers the possibility of definite and quick relief. The treatment of chronic constipation has all too frequently been confined to general measures. Usually the physician lays down a barrage of advice concerning proper habits, exercise, diet, and recreation. The patient listens and tries vainly to fit the ideal scheme into the limitations of his crowded existence. Often when he is able to comply with all of the requirements prescribed by the physician he is unsuccessful because of

the existence of the anal deformity which has been the subject of this discussion. The results of the treatment of the patients in this series have been satisfactory.

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The Effect of Aluminum Hydroxide Cream on Absorption from the Gastro-Intestinal Tract

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DURING the past year a number of reports have appeared in the literature concerning the value of colloidal aluminum hydroxide cream in the treatment of peptic ulcer and chronic colitis. Since aluminum hydroxide is employed extensively as an enzyme adsorbent, it appeared possible that when administered orally it might interfere with digestion by adsorbing gastro-intestinal enzymes. If this were true, its prolonged administration might be expected to lead to nutritional deficiencies.

The effect of adsorbing agents on the activity of a given enzyme depends on a number of interacting factors. A given adsorbing agent may quantitatively remove an enzyme from solution at one pH while it removes it incompletely or not at all at a slightly different pH. The order in which enzyme, substrate, and adsorbing agent are mixed also effects the degree of adsorption. Further, under certain conditions, an adsorbed enzyme may be as active as it is in the free state. Since the multiplicity of conditions encountered in the gastro-intestinal tract during normal digestion can not be duplicated in a test tube, results obtained in vitro can not be unequivocally used as a basis for anticipating in vivo results. Therefore, although preliminary in vitro experiments showed that aluminum hydroxide does not significantly alter the activity of trypsin or pancreatic lipase when the enzymes are permitted to act under optimum conditions, animal experiments were undertaken.

METHODS

In vitro experiments: The tryptic and lipolytic activity of a pancreatin preparation of known potency was determined with and without the addition of an excess of aluminum hydroxide. The non-protein nitro-

gen method described by Northrop (1) was used for measuring tryptic activity. Lipase was determined according to the method described by Cherry and Crandall (2).

In vivo experiments: Three dogs were given 500 grams of a standard diet daily for a period of 16 days (nitrogen content of diet 0.75%, fat content 3.5%). To insure uniformity, the diet was made up in a single batch large enough to last throughout the experiment. The experiment was divided into two eight day periods. During the first period the unsupplemented diet was fed (control period). During the second

TABLE I

Dog No.	Control Period—5 days			Aluminum Hydroxide Period—5 days		
	Total Wet Weight of Feces	Total Nitrogen	Total Fat	Total Wet Weight of Feces	Total Nitrogen	Total Fat
1	639	9.5	12.6	722	10.4	12.2
2	461	2.6	11.5	575	8.9	13.8
3	561	10.7	11.7	597	9.5	12.4

period 80 c.c. of a standard commercial aluminum hydroxide cream was mixed with the diet of each dog daily. A carmen "marker" was given with the meal on the fourth day and again on the eighth day of each period. All feces passed from the first appearance of the first dose of carmen until the disappearance of the second dose were collected daily.

Each day the total feces passed by each dog were weighed and thoroughly mixed, and aliquots were taken for the fat and nitrogen determinations. In the

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case of each dog all of the samples collected during each absorption period were pooled and the analyses were made on the composite samples. The samples for the fat determinations were preserved in alcohol; the samples for the nitrogen determinations were suspended in sulphuric acid as recommended by Peters and Van Slyke (3). Nitrogen determinations were made according to the Kjeldahl method; fat determinations according to a modification of Saxon's method (3). All determinations were made in duplicate.

RESULTS

In vitro experiments: The activity of the pancreatin was unaltered by the presence of the aluminum hydroxide cream.

In vivo experiments: It will be seen by consulting Table I, that the addition of aluminum hydroxide to the diet effected only the bulk of the feces. The differences in the nitrogen and fat content of the feces between the two absorption periods are all well within normal physiological variations. In fact, the constancy between the two periods and between the different dogs is striking. The bulk of the feces was increased by the addition of aluminum hydroxide cream in all of the dogs.

DISCUSSION

The dose of aluminum hydroxide cream administered in this study was comparable to the larger doses usually recommended clinically. The fact that it was administered in a single dose with the daily meal rather than in small divided doses should enhance the value of the results obtained. If gastro-intestinal enzymes were going to be inactivated as a result of adsorption, with a consequent disturbance in diges-

tion, the large single dose would be more apt to cause a disturbance than small divided doses. Although the system of demarkating absorption periods by the inclusion in the diet of inert materials which color the feces is not particularly sensitive, the difference between the two periods in the bulk of the feces is probably significant. The aluminum hydroxide itself, being largely unabsorbed, would contribute to the increased bulk, although in the case of dogs number 1 and 2 the increase was greater than could be accounted for on this basis. Aluminum hydroxide cream contains about 5% solid aluminum hydroxide. Therefore, during the 5 day period a total of only about 20 grams of dry material was added to the diet. The difference in weight in excess of that attributable to the solid aluminum hydroxide, is probably due to an increase in the water content of the feces resulting from the presence of the aluminum hydroxide.

SUMMARY

Since aluminum hydroxide is employed extensively as an enzyme adsorbent, it appeared possible that when administered orally it might interfere with digestion by adsorbing gastro-intestinal enzymes. Experiments conducted to test this hypothesis showed that relatively large doses of aluminum hydroxide cream did not alter the nitrogen or fat content of the feces of three normal dogs on a standard diet. This confirmed preliminary *in vitro* findings.

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The History of the Development of the Stomach Tube With Some Notes on the Duodenal Tube*

By

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and

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THE introduction of instruments of precision with their constantly changing additions and improvements frequently represent important stages in the development of a specialty in medicine. One need only refer to such instruments as the ophthalmoscope, laryngoscope, stethoscope, proctoscope, cystoscope and others as proof of this fact. Thus the stomach tube from the earliest times in its primitive form, to the present day with its many modifications and increasing possibilities has continuously played a peculiarly important role in the advancement of gastro-enterology.

Even previous to the discovery of the primitive tube, various practices were indulged in by the Romans to induce vomiting at the completion of a banquet in order to prevent the after effects of an overloaded stomach as well as to give place again for another

meal. At times emetics were employed but these seemed too uncertain in their results, and unpleasant as well. However, it was soon realized that it was only necessary to apply the finger to the throat to accomplish the same result. To escape the ill effects of these procedures Emperor Claudius and his guests were accustomed to allow the throat to be irritated with the "pinna" or vomiting feather at the completion of a banquet.

The celebrated medical historian Oribasius of the fourth century, A. D. fully described the methods employed in producing emesis at that time. Swinging the individual in a suspended bed was practiced until an artificial sea-sickness was produced. He likewise recommended as a substitute for the use of the finger, eight to ten goose feathers dipped in iris oil or cypress oil applied to the throat to induce vomiting. He also described an instrument consisting of a long feather

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glove-finger, ten to twelve inches in length, of which the lower two-thirds are to be filled with wood fibre while the upper third is to remain empty to receive the directing finger of the physician. The digital vomitorium was to be lubricated with the oils already referred to and introduced into the esophagus. This instrument was considered by Leube as the most primitive type of stomach sound.

Avicenna in his writings in the 11th Century had also advised the use of a similar apparatus for the evacuation of the stomach. In his work on poisonings, Hieronymus Mercurialis (16th Century) recommended the application of the *lorum vomitorium* to produce emesis. This instrument had especially been lauded by Scribonius Largus in conditions of opium poisonings. It dates as far back as the first Century. The *lorum vomitorium*, a poorly described instrument, consisted, according to Leube, of a leather strap treated with some nauseating tannic acid-containing substance which produced emesis when introduced into the esophagus due to its obnoxious taste.

The three methods described, namely, the pinna, digital vomitorium and *lorum vomitorium*, had as a common purpose the evacuation of the contents of the stomach.

A further step toward the development of the more modern tube was made possible as the result of the introduction of apparatus intended not only for emptying the stomach of its contents but also for removal of foreign bodies from the esophagus or forcing them into the stomach. The oldest instruments utilized for this purpose were short perforated metallic tubes so constructed as to clasp foreign bodies such as fish bones and thus to extract them. Leube cites Guilielmus Fabricius Hildanus whose great skill was recognized in removing foreign bodies from the esophagus with a perforated tube to which a small sponge was attached at its lower end. An advance was made by Hieronymus Fabricius ab Aquapendente in advocating the propulsion of foreign bodies into the stomach when there was no possibility of their extraction by mouth. He also devised an instrument for artificial feeding. This was accomplished through a silver tube covered with sheep's intestine to be utilized for patients affected with difficulties in deglutition. Thus as early as the 16th and 17th Centuries a new method of artificial alimentation was devised and a new principle established which has gradually led to the further development of the stomach tube and to its present day modifications.

Toward the middle of the 17th Century a new application of the tube made its appearance in Europe and was heralded as a marvelous therapeutic measure. It was variously termed stomach cleanser or brush, or "magenkratzer or magenraumer." This instrument was devised so as to apply treatment directly to the interior of the stomach. The stomach brush consisted of a long smooth flexible arched whalebone two to three feet in length tipped with an ivory button to which a tuft of silk cord, horse hair or linen was firmly attached. The instrument was passed down the esophagus into the stomach and applied as a cleansing apparatus. The remarkable success attained by means of this instrument spread rapidly through Europe and many reports concerning its use were published in England, France, Norway and Germany.

This method of treatment finally developed into an

actual form of so-called "Cure"; the instrument being kept in a church or convent and treatment practiced there under great secrecy.

Leube narrates the following interesting account of a Russian statesman upon whom the stomach brush was used: A Statesman who had returned from Russia and who had been in bad health due to the abuse of alcohol as well as from over-fatigue was advised by the King to enter a convent for treatment. The inmates of the convent were in remarkably good health, notwithstanding their ages; among them a priest of 115 years who was still able to read and write without the use of glasses. The statesman seemed greatly impressed by the sight of such healthy individuals and was encouraged to undertake treatment. After four weeks of treatment, under the usual medication, no relief was obtained. The monks then decided to undertake the "secret cure" which they had been accustomed to practice upon themselves. However, after arranging for the fee, the patient was required under oath to swear never to reveal the "Arcanum," the method which was to be undertaken to restore him to health. The "Arcanum" was none other than the stomach brush and treatment was instituted following certain preparations. Although the patient seemed extremely distressed by the treatment and squirmed, spat out and vomited and begged to have the treatment discontinued, he was nevertheless forced to drink water and the brush was again applied until the stomach was entirely cleansed. This was undertaken in the morning and was continued at 24 hour periods for eight days. At the end of this time, the patient was quite able to continue on his journey in good health and in good spirits. Finally the secrecy with which this method of treatment was surrounded disappeared and its use was generally advised even for healthy individuals as a prophylactic measure with the object of attaining a long life and as a curative measure for all stomach troubles. The stomach brush was now manufactured in various places and was very commonly used by patients.

The poor results attained from this form of treatment in some instances and the fatalities that occurred especially in certain cases of carcinoma of the stomach gradually led to its disuse, and the instrument in the form of whale bone-sound tipped with a sponge was continued to be utilized only for the treatment of esophageal diseases and especially in obstructive affections. The famous case of Thomas Willis is interesting. His patient had difficulty in swallowing which gradually increased to such a degree that he was no longer able to swallow food. Death seemed imminent. Willis prepared an esophageal sound and the patient was given food which was thrust down the esophagus by means of this instrument. He received treatment in this manner for 16 years. Abercrombie later employed a silver esophageal sound with an oval knob at its tip for this purpose with great success. The problem which had not been satisfactorily solved up to this time and still confronted the physicians of this period was that of artificial feeding as well as the possibility of introducing remedies into the stomach when deglutition was impeded and likewise when the contents of the stomach required complete and prompt removal than was possible with emetics. This could only be accomplished with a sound of tubular form and of sufficient length as to extend into the stomach.

Hieronymus Capiwakeus and Fabricius ab Aquapendente were among the first to attempt to apply this form of treatment. Capiwakeus employed a tube with an animal bladder attached at its upper end containing a nutritive fluid which was expressed into the stomach. Fabricius ab Aquapendente introduced a small silver tube covered with lamb's intestine through the nose into the esophagus for purposes of artificial feeding.

A further development of significance was achieved when Van Helmont in 1646 discovered a method of manufacturing flexible catheters of leather which naturally could be made of considerably greater length and by Boerhaave (1668 to 1738) who suggested the use of a flexible stomach tube in cases of poisoning in individuals unable to swallow antidotes.

On March 21, 1776, John Hunter read a paper on "Proposals for the Recovery of Persons Apparently Drowned" in which he advised the use of "a syringe with a hollow bougie or flexible catheter of sufficient length to go into the stomach and convey stimulating matter into it without affecting the lungs."

Again 17 years later (1793) he published a paper read September 21, 1790, on "A Case of Paralysis of the Muscles of Deglutition, Cured by an Artificial Mode of Conveying Food and Medicines into the Stomach" in which he reported the case of John S., a patient of 50 years of age who had suffered with a paralysis of the muscles of deglutition which deprived him of the power of swallowing. Many forms of treatment were given without success and the administration of food and medication was advised by Hunter through a hollow flexible tube passed into his stomach. This was undertaken by him and given twice daily. The paralysis gradually disappeared.

In his Inaugural Thesis, Alexander Monroe, Jr., in 1797, suggested the use of the tube and syringe in cases of poisoning for the extraction of the poison from the stomach and for the introduction of food into the stomach in cases of dysphagia in human beings. He likewise pointed out that his father as early as 1767 had employed a flexible tube to remove fermenting fluids and gases from the stomach of cattle affected with esophageal spasm causing great distention and in whom vomiting was impossible.

In France both Renault and Dupuytren followed in 1803 with the suggestion for the employment of a flexible tube of sufficient length to reach the stomach connected with a syringe to aspirate the stomach in case of poisoning.

The credit for the introduction of the stomach tube into American Medicine is due to Philip S. Physick, Professor of Surgery in the University of Pennsylvania. Physick published his paper in 1812, entitled "Account of the New Mode of Extracting Poisonous Substances from the Stomach."

He declares that he employed the tube in washing the stomach of twins three months old who had accidentally been given an overdose of laudanum by their mother. He employed a large flexible catheter for this purpose. It was passed into the stomach and a drachme of diluted ipecac was then injected with a syringe. He then withdrew the fluid contents of the stomach through the sprig and injected warm water, which was again withdrawn. As a result one of the children was saved, the other died. Physick states that the idea of washing out the stomach with a syringe and tube in cases in which quantities of laudanum or other

poisons had been swallowed occurred to him at least twelve years before and he had constantly for many years recommended it in his lectures. In the year of 1809 his nephew, Dr. Dorsey, practiced lavage in a case, but the patient had swallowed the poison twelve hours before he was called, so that he did not succeed in saving life.

Of interest in this connection is a letter published by Physick in the same volume of *The Eclectic Repository* in which he states "I am happy in having called the attention of the profession to a mode of treatment not before used in this country, at least within my knowledge; but I have now an act of justice to perform, in ascribing the merit of the invention to Doctor Alexander Monroe, Jr., of Edinburgh, who published it in his inaugural thesis, in A. D. 1797. Of this circumstance I was entirely ignorant when I sent you my paper, and probably should still have remained so, had it not been mentioned in his book of *Morbid Anatomy*, a work which has but very lately come into my hands." Physick's priority as to the discovery of the stomach tube was apparently vigorously contested in this country. However, the controversy was by no means limited to this country but was even more vigorous and raging in England where contention ran high as Jukes, Bush, Evans and Reed, each claimed priority for the discovery about the same time.

As a further development in the chain of events a new instrument for the evacuation of the stomach was demonstrated by Mr. Reed of Hosmoden Lane, Kent, to Sir Astley Cooper and interested physicians at Guys Hospital on November 21, 1823. "Mr. Reed was in the theatre during the whole of the time and superintended the use of the instrument; on quitting he received the unanimous applause of those present. Sir Astley Cooper, just after the experiment had been tried, looking at what had been removed from the stomach, said that the instrument would do well for an alderman after a city feast."

The important improvement in the Reed instrument was in the special syringe, so constructed with two valves, that the need of removing the syringe in the process of gastric lavage could be avoided.

About the same time Weiss, an instrument manufacturer, developed and patented a new type of pump for the following purposes: (1) for emptying the stomach of poisons. (2) for removing water in drowning before applying artificial respiration, (3) for giving enemata.

The apparatus was widely used especially in Germany and many references are made to it in the German and English literature. There are always difficulties encountered in any attempt to establish the validity of priority in medicine as the development of a discovery is often so gradual and frequently enveloped in a series of events gathered from many sources, that it may become impossible to name any single individual who should receive the entire credit. This is especially so regarding the discovery of the stomach tube.

If we weigh the evidence in evaluating the priority in regard to the discovery of the stomach tube, it is quite clear that Boerhaave was the first to suggest the use of a flexible tube to be passed into the stomach as a method of treatment but there is no evidence that he ever employed it for this purpose. In 1776, however, John Hunter suggested the use of the stomach tube and in 1790 reported its use as a method of ali-

mentation in a case of paralysis of the muscles of deglutition. Renault and Dupuytren in 1803 published the description of a tube which they had perfected and Alexander Monro, Jr., in 1797, likewise suggested the use of a tube and syringe as a suitable means of extracting poison from the stomach; it does not appear, however, that any practical application of this apparatus was made in cases of poisoning or other conditions.

Philip Syng Physick advised lavage of the stomach with a tube and syringe in 1800, but his first publication only appeared in 1812. The reports of Jukes, Bush, Evans and Reed appeared later (1822) and therefore need not be considered in determining the matter of priority. Physick has been commonly acknowledged as the discoverer of the stomach tube especially in this country and one of us has formerly maintained this view and published a paper to this effect. His publication appeared in 1812, although he employed the tube in 1800. Further evidence, however, establishes the fact that the credit of this discovery of the stomach tube is due John Hunter.

In summary the conclusion is arrived at that John Hunter was the inventor of the stomach tube and was the first to make use of it in England; that the tube was first introduced into America by Physick and in France by Dupuytren and Renault. Following the rival claims of priority by Jukes, Bush, Reed and Evans and the appearance of the important publication of Alcock which followed in 1823, the tube was soon forgotten and was not generally employed until 1869, when Kussmaul, in his classic publication, suggested its use in the treatment of gastric dilatation.

Only a few publications of note appeared in the interim, that of Somervail in 1823, Arnott in 1829, both advising syphonage as a method of performing gastric lavage instead of by suction.

Kussmaul published his observations in 1869, and laid the foundation for an exact means of diagnosis in gastric disturbances. In this valuable paper Kussmaul describes difficulties encountered in the treatment of advanced forms of dilatation of the stomach due to stricture of the pylorus.

He remarks: "Very exceptionally was it possible to obtain any results in the treatment of this dreadful disease. As a rule it may hardly be possible even to expect an amelioration of the symptoms, and never possible to produce a cure."

Realizing the serious state as well as dire distress in a country girl of 20 years, in the wretched stage of vomiting the thought occurred to him that he might bring about relief by means of lavage of the stomach.

The introduction of the stomach tube, the pumping out, and washing were usually easy. Three liters of acid, dirty-gray, sarcina-containing fluid, with particles of food of all kinds undergoing softening and decomposition were withdrawn. This was first accomplished on July 22, 1867.

Although most enthusiastic over this new method of treatment, Kussmaul recognized its limitations. He realized that only when slight constriction of the pylorus existed was he able to obtain a cure in cases of dilatation of the stomach by lavage. In malignant stenosis of the pylorus and in cases of cicatricial contraction relief only could be afforded, and not cure. He says: "Naturally, it is impossible to expect a cure of a dilated stomach by means of lavage when the pyloric orifice is narrowed to such an extent that it

will hardly admit even as much as a goose quill." It is here that Kussmaul points out the possibility, that surgery would at some future day bring relief to these cases, and it is possible, as Fleiner suggests, that perhaps it may have been the inspiration of this remark that led Billroth at a not very distant date to attempt to cure intractable forms of gastric disease by surgical measures. Thus a new method of treatment, this epoch-making work of the great master Kussmaul, furnished the impetus for the study of gastric diseases according to modern scientific methods and led to the stomach-tube, not only as a new method of treatment but also of diagnosis.

Great credit is due Kussmaul who was the first to publish a definite method of treatment by means of gastric lavage for dilatation of the stomach and thus by creating renewed interest in the stomach tube established the beginning of modern methods of diagnosis and treatment of diseases of the stomach.

Since it was soon discovered that as the result of suction with the stomach tube trauma was often produced sufficient to withdraw bits of gastric mucosa from the stomach, syphonage, which had already been advised by Somervail and Arnott was again introduced by Ziemssen, Rosenthal, Rosenbach, Hodgen, Leube and Jurgensen.

Jurgensen likewise recommended a soft rubber tube and explained the method of introduction of the stomach tube, the position to be assumed by the patient as well as the method of practicing syphonage. This contribution must be classed as a distinct advance in the therapeutics of gastric diseases. Jurgensen utilized the rubber tube terminating in a perforated ivory ball. The bulb was guided by means of a wire stylet.

In order to more readily facilitate gastric lavage, double recurrent stomach tubes were now constructed by both Auerbach and Ploss. However, these were soon found impractical due to their large size and Hemmeter later developed a more useful tube of this type. It was after but an interval of five years, that Ewald and Oser introduced the soft rubber tube independently of each other which was to be passed without the aid of a mandurin. Ewald demonstrated, by chance, that if a rubber tube was sufficiently firm it could be introduced without difficulty. In a patient who had swallowed prussic acid with suicidal intent and who was brought to Frerich's Clinic, evacuation of the stomach had to be accomplished immediately. A stiff tube was not at hand and Ewald proceeded at once to remove a piece of rubber gas tubing, rounded off the sharp edge and cut out two eyelets. The tube was oiled and although the patient was unconscious he succeeded in passing the tube into the stomach.

Ewald and Oser were therefore the first to demonstrate that the soft rubber tube could be easily introduced into the stomach without the aid of a mandurin. While Kussmaul drew attention to the therapeutic value of the stomach tube, it remained for Leube in 1871 to point to the value of the stomach-tube as a diagnostic measure and also to emphasize the fact that it is impossible to arrive at a proper conclusion concerning the nature of gastric conditions without the use of this instrument.

Twelve years later (1883), Leube established his test meal as a means of determining the state of motor sufficiency of the stomach, concluding that a normal

stomach should be empty seven hours after the ingestion of a meal of soup, broth, steak and bread. This test of Leube's is recognized today as a most valuable means of determining variations in the motor function of the stomach. Leube also at this time analyzed the gastric secretion obtained through the stomach tube, by utilizing mechanical influences as for instance from the irritation produced by the prolonged use of the tube; by chemical influences, the ingestion of soda-water; and by thermic stimulation in swallowing ice-water. Riegel (1881) showed the difficulties encountered in obtaining gastric juice by stimulating the gastric secretion by means of ice water, according to the method of Leube, as but minimal quantities are thus obtained. He therefore advised the withdrawal of the gastric contents through the tube after his well known test dinner of soup, beefsteak, bread and mashed potatoes and also established the fact that the most favorable time for removal is at the height of digestion. He demonstrated here, too, that the absence of hydrochloric acid is a usual occurrence in cancer of the stomach even though this acid is at times absent in other conditions.

In their classical work on the "Physiology and Pathology of Digestion" (1885-1886) Ewald and Boas presented their experiments regarding the appearance of free hydrochloric acid and lactic acid in the stomach contents obtained through the tube and also drew attention to other important factors connected with the chemistry of gastric digestion. Ewald here fully described his test breakfast and presented its advantages as well as its importance in the diagnosis of gastric disease. The expression method of obtaining gastric juice is also described and was adopted as the simplest method of obtaining this secretion.

A further significant advance was made by the introduction of duodenal intubation, the possibilities of which are still in their infancy and are constantly widening. The first attempt at recovering duodenal secretion was undertaken by Boas in 1889, who was occasionally able to obtain duodenal contents by introducing the stomach tube in the fasting state following massage of the right upper abdomen. Boldyreff could likewise at times obtain this secretion by administering a fatty meal after which regurgitation of bile and duodenal contents would occur into the stomach.

Hemmeter was the first to actually attempt instrumental intubation of the duodenum though Turck had previously claimed to have succeeded in accomplishing this by means of his so-called "gyromele" which was primarily intended to outline the boundaries of the stomach by the aid of palpation over the abdominal area. Hemmeter passed a balloon into the stomach which was then inflated; following this a rubber tube was inserted over a groove on the upper surface of the balloon and was thus guided into the duodenum. His method, however, proved to be difficult and impractical.

It was not until 1909 that the duodenal tube of the present day type was introduced independently by both Einhorn and Gross. The tube was afterward modified by Rehfuss and others but these simply represent variations of the original Einhorn model. All consist of small soft tubes with tips so weighted as to rapidly pass into the duodenum. A modification of importance is the tube introduced by Levin in 1921, consisting of a smooth catheter entirely of rubber without the addition of a metal tip. It has the great

advantage in that it can be inserted both through the nostril as well as by mouth.

In the introduction of the duodenal tube another new era in the advancement both as to diagnosis and treatment in gastro-enterology was inaugurated.

While duodenal intubation was at first employed only for purposes of securing duodenal secretion it was soon recommended for duodenal and intestinal lavage. A further advance was made when Lyon in 1917 instituted his method of non-surgical biliary drainage by means of the duodenal tube with a solution of magnesium sulphate. This procedure is now successfully practiced both as a diagnostic as well as a therapeutic measure. Fractional gastric analyses so commonly utilized nowadays have likewise been made possible by means of the duodenal tube.

Duodenal intubation is now recognized as an extremely valuable measure in nourishing patients affected with certain digestive disorders associated with nausea or persistent vomiting. It has also been found very useful in the treatment of certain forms of peptic ulcer.

The duodenal tube is now largely employed following surgical procedures for purposes of aspiration of gastric and intestinal contents and for introducing fluids and nourishment into the digestive tract, for overcoming persistent vomiting and distention and is likewise a valuable measure in such conditions as gastric dilatation, ileus and localized peritonitis.

Continuous suction can be practiced through the tube and has been especially helpful in special types of intestinal obstruction as well as an aid following operative procedures for intestinal obstruction. The literature pertaining to duodenal intubation has become extensive and innumerable publications have appeared during the past years describing many important developments related to the digestive processes, in health as well as in disease, in which this tube has played a significant role. It would be beyond the confines of this paper, however, to attempt to supply even an outline of this extensive literature. Among the important contributors in this field other than those already referred to are Jutte, Palefski, Simon, Soper, Buckstein, Smithies, Ward, White and Paine and Wangenstein.

One cannot dismiss this historical sketch without a brief word regarding another type of tube through the introduction of which important diagnostic information regarding disturbances of the esophagus and stomach has been obtained, namely, the esophagoscope and gastroscope.

Kussmaul in 1868 was the first to attempt gastroscopy. He employed a rigid tube which he was able to insert into the stomach, but could not visualize this organ satisfactorily. Miculicz was the originator of the modern instrument. He was enabled by means of this instrument which was constructed somewhat on the model of the cystoscope to actually visualize the interior of the stomach.

In 1895, Rosenheim developed a new type of gastroscope which was further improved by Rewidzoff in 1897 and still further by Kelling. Chevalier Jackson modified this instrument which was further improved by Sussman.

On account of the difficulties encountered in manipulating these instruments successfully, gastroscopy was abandoned until 1922 when Schindler developed

his new instrument. This was, however, difficult to insert due to its rigidity and not until 1932 did he announce his newly constructed flexible tube which can be inserted without great difficulty or danger and by means of which an exceedingly satisfactory view of the stomach can be obtained. The development of esophagocopy has been greatly aided by the instruments devised by Killian, Hill, Jackson, Einhorn and others. It has enabled the gastro-enterologist to visualize all portions of the esophagus and thus has been of great value as a method of diagnosis and has likewise materially assisted in direct treatment as in the removal of foreign bodies, the direct application of remedies as well as in the removal of specimens for microscopic examination.

And thus we conclude a chapter in the history of

the stomach tube from the earliest times, beginning with the pinna and stomach brush to the present day tube with its modern improvements and many sided accomplishments.

The development of the tube into its present form portrays in a large measure the great advance made in our knowledge of digestive diseases. The interesting papers of Major and of Paine also bear this out.

As in other specialties in medicine, instruments of precision have often played a major role in their development, so too in gastro-enterology, the tube has assumed a similar role. It is possible that in the future as in the past, it will continue to lead the way to still further achievements in our knowledge of digestive diseases.

The Therapeutic Application of Acidophilus Milk in Constipation of Children*

By

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THE very early recognition of constipation is attested to by the frequent references to the purge in ancient medicine. Various systems of classification of constipation have been proposed. For a discussion of this phase of the subject the reader is referred to a recent publication from this laboratory.[†] Bayliss and Starling (1899) and Cannon (1902) were apparently among the first to study the movements of the intestine. By the use of the X-ray administration of bismuth, and other devices, there has been established an elaborate mechanism which involves the normal rhythmic segmentation, peristalsis of the small intestine, the haustral movements, antiperistalsis and slow and rapid colonic waves in the large intestine. A disturbance of this mechanism must be regarded as an important factor in intestinal stasis, or the reverse of this condition.

The type of food ingested may greatly influence the frequency of evacuation of the intestine. Thus, a diet containing an appreciable amount of fiber is necessary before any regularity of evacuation can be accomplished. This has again been shown by the recent researches of Cowgill and Anderson (1932), and Cowgill and Sullivan (1933). Diets having very low fiber content, that is, so-called "low-residue" diets, lead to intestinal stasis. Again, during starvation, the bowel evacuation may not occur for periods of weeks. In determining the cause of constipation in any case, it is of utmost importance to take into consideration the nature of the subject's diet, including adequacy of the

vitamin content. It has been shown by some investigators that vitamin B complex, for example, plays an important role in the regulation of intestinal movement.

Diet is of special importance in its relation to intestinal evacuation in infants, since minor deviations from the proper regimen very frequently lead to quite severe intestinal disturbances. Nurslings are often constipated because of a low total solid intake in the diet. Frequently inadequate amounts of breast milk result in constipation. Similar problems present themselves in artificially fed infants. A striking example of constipation due to inadequate amounts of food is that of hypertrophic pyloric stenosis and pylorospasm where obstruction (functional or organic) of a severe type interferes with the passing of food from the stomach into the intestinal tract. Artificially fed infants are subject to some degree of constipation when the carbohydrate or fat content of the formula is deficient in amount. This accounts for the frequent use of malt sugar preparations in infant diets. On the other hand, over-feeding may result in excessive intake of protein and fat, which leads to a bulky residue of calcium soaps, which in itself causes constipation. As simple a factor as inadequate fluid intake may result in constipation in infants, although this cause of stasis is more frequently observed in older children and adults.

Mechanical factors also play a very important rôle in controlling the normal functioning of the bowel. In dealing with infants one is confronted all too frequently with constipation of mechanical origin. The relatively long large intestine of the infant, with its resultant large "omega" loop, and the sharp turns so often found in the sigmoid region, may offer obstruction to the fecal stream and predispose to constipation.

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*From the Department of Eastern Long, Yale University, New Haven, and the Child Hospital, Portland.
†The Journal of Pediatrics and the Therapeutic Application. Rettger, L. F., Weinstein, W., Bogin, M., and Weiss, J. E. Yale University Press, 1933.
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Hirschsprung's disease is an outstanding example of the effect of mechanical ineptitude in constipation. Other mechanical factors, such as congenital bands, may cause obstruction, and in older children post-infectious peritoneal bands or adhesions may result in varying degrees of stenosis of the intestinal lumen. More rarely, mechanical pressure upon the intestine may be due to neoplastic masses or to an enlarged or displaced viscus as, for example, the spleen, kidney or uterus. Interference due to enteroptosis occurs more frequently in older children than in infants, but volvulus and intussusception must be considered in constipation in infants.

Conditions which are essentially systemic in nature may cause constipation by an indirect effect on the intestinal tract. Thus, the atonic state of the abdominal and intestinal musculature in rickets in infancy predisposes to constipation. Similarly, intestinal stasis is also a frequent finding in cases of cretinism and in various nervous and mental disturbances.

Mention should be made also of the constipation ascribed to faulty habit. Not infrequently a child is too busily engaged in play to heed the normal desire for defecation, with resultant retention and consequent dehydration of the fecal mass. Injudicious parental management may result in situations of emotional stress, so that a child, endowed with sufficient negativism, and sensing the veritable obsession of the parent to constipation in childhood, may wilfully retain the feces.

In 1922, Rettger and Cheplin first recommended the use of acidophilus milk in constipation in adults. In 1933, Weinstein, Weiss, Rettger and Levy, and in 1935, Rettger, Levy, Weinstein and Weiss reported favorable results with acidophilus milk in the treatment of a large number of cases of constipation in adults. No attempts were made to treat this disorder in children, but it seemed that, in view of the fact that children are as a rule more reactive to various influences, acidophilus milk should be of much value in the treatment of constipation in childhood. With this in mind, the investigation reported here was undertaken.

METHODS

Children ranging in age from 10 months to thirteen years were included in this investigation. The authors were fully aware of the pitfalls into which one may easily slip in attempting to determine the cause of constipation. Efforts were made to eliminate mechanical, dietary, systemic, nervous and certain other causes of the disorder. Each child was observed for a period of at least three weeks before treatment with the acidophilus milk was begun. During this observational period, attempts were made to make the diet as nearly correct as possible nutritionally. In cases where there appeared to be an indication of mechanical stasis, X-ray pictures were taken following barium enemas. Attempts were also made to enlist the aid of the mothers of the children in trying to develop proper habits.

If, at the end of the period of preliminary observation there was no marked improvement in the constipation, the children were given one pint of acidophilus milk daily. In instances where infants were still on milk-containing formulas, the acidophilus milk was substituted for the sweet milk, all of the other ingredients in the formula being left as they were. The regular feeding schedule was not interrupted or

changed in any manner. For the older children the acidophilus milk was added to the diet in place of one pint of the sweet milk which most of the children were taking daily. No changes were made in the diets of the older children after the treatment with acidophilus milk was begun.

Stool examinations for *L. acidophilus* were made weekly in every instance, according to the technic previously described by Weinstein, Weiss, Rettger and Levy (1933). At least two stool cultures were made in each case before treatment was started. None of the subjects harbored demonstrable *L. acidophilus* in the intestine before treatment. All of the children were given the acidophilus milk for a period of at least twelve weeks. If, after withdrawal of the cultured milk from the diet, there was no recurrence of the constipation no further treatment was given; when, however, there was a return of the complaint the subject was again treated for a period of twelve weeks, after an intervening "rest" period of from two to four weeks. This alternate milk feeding and milk exclusion regimen, first definitely instituted by Weinstein et al (1933), was carried out until there was no return of the constipation for a period of at least twelve to sixteen weeks after cessation of treatment. In instances where only one feeding period was required, the children were under observation for at least six months after withdrawal of the cultured milk from the diet. The results were recorded as positive for the individual cases when there was no recurrence of the constipation during this period.

RESULTS

The acidophilus milk treatment was carried to completion in 27 children suffering from constipation, 22 females and 5 males. Ten other children all under three years of age were also treated, but for various reasons, such as difficulties experienced in administering the milk, were dropped from the investigation before the treatment had been carried on for four weeks. In a few instances the mothers complained of the milk being regurgitated soon after being taken. In these cases there was apparently some degree of intolerance for the acidophilus milk. No instances of marked distaste for the milk, or of vomiting after taking it, were observed in any of the children that were over four years of age.

Of the 27 children in which the treatment was carried to completion, 22 reacted favorably to the milk, 3 failed entirely to respond, and 2 gave results which were irregular and of a doubtful nature. Of the 22 children who reacted favorably 14 became so-called "implanters," that is, they carried the *L. acidophilus* organism in large numbers in their intestine for at least sixteen to twenty weeks after cessation of treatment. Eighteen of the responsive cases were treated for only one period of twelve weeks, while the remaining 4, together with the 2 doubtful cases, were first given the milk for one period of twelve weeks, then allowed a "rest" period of four weeks, at the end of which they again took the milk for twelve weeks. In the last-named cases the constipation returned during the first two weeks after cessation of treatment. After the conclusion of the second treatment period 4 of these subjects remained free from constipation during a period of at least six months. The other two still gave a doubtful reaction.

Owing to the unduly large amount of space required for full case histories of all of the subjects which were treated with acidophilus milk, descriptions of only one of the positive and one of the negative cases are presented here.

Case 1. J. S., male, age 10 months. Mother reported that the child had been constipated since birth. Certain corrections were made in the dietary before acidophilus treatment was begun, but without any beneficial effect. Following a preliminary observation period of four weeks, acidophilus milk was substituted for the plain milk in the daily diet. No improvement in the bowel condition was noted during the first two weeks of treatment, and *L. acidophilus* could not be detected in the stools. The mother had been instructed to give the child an enema of physiological salt solution when natural evacuation did not occur. In the third week the mother reported that the child had moved its bowels several times without the use of the enema. At the end of the third week *L. acidophilus* was present in the feces to the extent of about 25 per cent of the total viable flora. During the next nine weeks there were at least one or two normal stools daily, and the *L. acidophilus* content of the intestine varied between 60 and 95 per cent. Treatment with the milk was discontinued at the end of this twelve week period.

Within two weeks the constipation returned with its former severity, and no aciduric bacilli could be detected in the stool cultures. Acidophilus milk treatment was resumed at the end of the fourth week following its discontinuance. Within a week there was unmistakable improvement in the patient, and by the end of the second week the mother reported the child as having at least two natural movements daily. Stool examinations revealed an acidophilus count of 90 per cent of the total number of viable intestinal bacteria. The treatment was again continued for a total of twelve weeks, during which time there was no return of the constipation, and the *L. acidophilus* content of the colon remained high. At the end of this second acidophilus milk feeding period the milk was again omitted from the diet. Subsequent observation over a period of six months revealed no return of the constipation, and stool examinations showed a high *L. acidophilus* content, in spite of the fact that no acidophilus milk was being administered at any time during this entire period. The case was considered, therefore, as having reacted positively, and as having become an "implanter." When the child was seen again, one year after cessation of the last milk treatment, the mother reported that there had been no recurrence of the constipation. No stool examination was made at this time.

Case 2. A. G., male, age 8 years. The mother reported that this child had been constipated for four years. Attempts were made to correct the diet and to develop proper habits in this patient, without success. The various known causes for constipation in children were eliminated. No *L. acidophilus* was demonstrable in the stools during the observation period. The patient was given one pint of acidophilus milk daily. There was no relief from the constipation in the first four weeks of treatment. The lactobacillus count of the feces varied between 10 and 50 per cent of the total viable organisms during this period. Since no relief had been obtained, the amount of milk ingested daily was increased to one quart. Observation for a period of six more weeks showed no relief from the constipation. *L. acidophilus* at no time constituted more than 50 per cent of the intestinal organisms during this period. At the end of ten weeks of unsuccessful treatment the case was released.

DISCUSSION AND SUMMARY

Twenty-seven children ranging in age from ten months to thirteen years were carried through full treatment with acidophilus milk, for constipation.

Twenty-two of the group were completely relieved of intestinal stasis soon after the beginning of treatment; in this group there was no recurrence of the constipation for a period of at least four to six months after withdrawal of the acidophilus milk from the daily diet. Fourteen of the successfully treated individuals were classed as "implanters," since they continued to harbor *L. acidophilus* in the intestine for at least four months without the use of the cultured milk. In three of the children there was no relief from constipation even after treatment was continued for comparatively long periods. Two individuals gave doubtful responses, showing beneficial effects at one time and none at another. These reversals in bowel condition could not be correlated with any changes in the individual bacterial flora.

We wish to stress again the care which must be taken in experiments of the type reported here, to eliminate as far as possible all of the common causes of constipation in infants and older children. It is possible that in some of the cases which are included in this report a common cause of constipation may have been overlooked. It is our belief, however, that with a preliminary observation period of three to four weeks, with adjustment of the diet and elimination of all possible mechanical factors, most of the cases treated with acidophilus milk were suffering from constipation of unknown origin.

Milk to which a definite amount of lactic acid has been added has been prescribed by various pediatricians for constipation and other intestinal disturbances in children. Some persons may attempt to explain the favorable results obtained in the cases reported here as being due to the mere feeding of acidified milk. Evidence that the acid in acidophilus milk does not play a major part in the beneficial effects obtained in the treatment of constipation in adults has been presented by Kopeloff (1926). A similar conclusion was arrived at by the Orla-Jensens and Winther (1935-36). In the experiments reported here definite correlations could be established in almost every instance between the degree of relief from the constipation and the concentration of *L. acidophilus* in the lower intestine. When there were few or no aciduric organisms in the feces there were no indications of relief from constipation; conversely, when *L. acidophilus* constituted a large majority of the intestinal organisms, the patient experienced marked or complete relief from the constipation. Further evidence that the beneficial results were due largely to a change in the intestinal flora appears to be given support by the fact that a number of the children were free from intestinal symptoms long after acidophilus milk had been withdrawn from the diet. Stool examination showed that these individuals harbored *L. acidophilus* in the intestine, and most of them in large numbers.

Acidophilus milk is a wholesome food, in addition to being an effective agent in altering the intestinal flora. In view of the very fine curd which it possesses and the consequent ease of digestibility, it should be far superior even to sweet milk in the feeding of infants suffering from intestinal disturbances. The curd of acidophilus milk may be assumed to be of even finer consistency than that of artificially acidified milk, because the acid is formed slowly in the former and there is a continuous and slow precipitation of the protein of the milk. In using acidophilus milk in place

of ordinary sweet milk in the artificial feeding of infants, several facts must be borne in mind. First, that the prevailing brand of market acidophilus milk does not contain the same amount of fat as ordinary (market) sweet milk, and second, that part of the lactose has been removed by the organism. These facts must be taken into consideration in calculating the caloric value of the prescribed diet.

The authors are fully appreciative of the difficulties involved in a clinical experiment of this kind. The marked influence upon psychic factors of the administration of any substance, be it inert or potent, is always a problem in itself. We attempted to eliminate errors here by the use of preliminary periods during which enemata of saline solution were recommended, and in which the parent was informed that the disturbance was remediable, if regularity of bowel habit was encouraged, and the administration of fruits, vegetables and other standard laxative foods was carried out. Cases which responded to this manner of dietary correction were eliminated from the experiment.

The question of feasibility of administering soured milk to children and infants, raised by several parents at the beginning of the individual experiments, was not particularly provoking. Whereas, in a few instances we found it necessary to sweeten the milk slightly with chocolate syrup, a large majority of the children readily adapted themselves to the acidophilus milk, and in only one instance was its administration entirely abandoned because of the child's refusal to submit to it.

The question of cost raises a more difficult problem. Proper treatment of a case of true constipation necessitates prolonged and regular administration, and in the event of recurrence after cessation of treatment, a repetition of the 12 weeks' course. Our results followed close supervision of the cases over prolonged periods of time, with constant advice to the parents—a procedure of considerable expense in private practice. Against this cost one should weigh, however, what appears to be a permanent cure, at least in the cases in which the "implantation" of *L. acidophilus* results in complete relief of intractable constipation.

The authors wish to express their appreciation of the cooperative spirit of the personnel of the Bridgeport City Dispensary, which made available the clinical material for this experiment; and in particular to thank the Board of Directors, the Clinic Supervisor, the resident medical staff, and the nurses of the children's clinic.

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Benign Ulcer of the Gall Bladder*

By

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BENIGN localized ulceration of the gall bladder, not the result of pressure necrosis from calculi, is apparently a rarely observed disease at the present time. It is interesting to note in a study of the medical literature that in the present era of widely advised and accepted gall bladder surgery only occasional cases have been reported (one case cross indexed as such in the past twelve years in the *Index Medicus* (1)). As evidence of the modern experience in this connection Graham (3) states in reference to cholecystitis "in our experience we have never seen complete loss of epithelium as a result of inflammation" and Boyd (2) says "it is remarkable how intact the epithelium may be in the worst gall bladders." Yet during the period of the early development of biliary tract surgery in which there was considerably more hesitance in the acceptance of this form of treatment, ulcer of the gall bladder was seen with sufficient frequency to warrant detailed discussion in certain of the publications of the time. The most thorough consideration of the subject found is in the monograph *Diseases of the Gall Bladder and Bile Ducts* (published in 1904) by Sir Arthur Mayo Robson (4) who points out that ulcers

may be found associated with stones, typhoid fever, cholera, and primary carcinoma of the gall bladder. As complications of ulceration he cites clinical examples of stricture, perforation, fistula, peritonitis, hemorrhage, septicaemia, and pyaemia. In his cases the complications were, in general, the precipitating factor which led to the discovery of the lesion. In the present case it was an incidental finding at operation.

CASE REPORT

A 32 year old white farm wife came for examination because of right upper quadrant pain of twelve months duration. There was a history of mumps and measles in childhood. In adolescence there were several episodes of moderately severe right lower quadrant pain with associated constipation but no nausea or vomiting. These lasted usually from one to two days and required bed rest. She was married at 22 and had a child at 24, following which she began to gain weight slowly. She was troubled with constipation since childhood and when seen was using laxatives two or three times weekly. During the twelve months before admission she had been bothered with attacks of right upper quadrant pain which came at irregular intervals, which were worse at night, not associated with nausea or vomiting, but which did radiate to the tip of the right shoulder blade.

*Van Ravenswaay Clinic.
 Submitted September 11, 1937.



Mucosal surface of gall bladder showing ulcer and stone in cystic duct.

Physical examination revealed a moderately obese white female in no acute distress. The pupils were equal and reacted normally to light. The nose and throat were negative. The heart and lungs revealed no abnormalities on physical and fluoroscopic examination. The blood pressure was 120/80. There was moderate right upper quadrant tenderness localized in the region of the gall bladder, and also right lower quadrant tenderness near McBurney's point. The pelvic and rectal examinations were negative and the reflexes not remarkable.

Laboratory examination revealed the following: Blood: red blood count 3,200,000, hemoglobin 65 per cent and white blood count 5600. Urine: acid, no albumin or sugar, sediment negative. A gastric analysis showed 16 degrees free acid 45 minutes after an Ewald meal.

X-ray: Films at 4 and 8 hours after the administration of intravenous dye showed no evidence of a gall bladder shadow. No opaque calculi were seen. A barium meal entered the stomach through a normal esophagus and the stomach and duodenal cap filled and emptied normally without evidence of intrinsic or extrinsic lesions.

A diagnosis of cholecystitis, probable cholelithiasis, and recurrent appendicitis was made and operation advised. Following a period of preoperative preparation cholecystectomy and appendectomy were done. Following this there has now been symptomatic relief for a year.

Pathological report (Dr. Thomas J. Kelly): Gross examination: The gall bladder is enlarged to two times the usual size, is greyish white in color, and has a definitely thickened wall. On the posterior surface of the fundus there is a deep ulcer involving the submucosa and muscularis. The ulcer has an indurated prominent edge and measures 1 centimeter in length, 0.5 centimeters in width, and 0.3 centimeters in depth. There is a single yellow mulberry shaped stone 0.5 centimeters in diameter in the mouth of the cystic duct. Microscopic examination: Sections through the wall of the gall bladder in the region of the ulcer reveal its edge to be composed of dense fibrous tissue while the base shows a mass of blood pigment, lymphocytes, and fibroblasts. Immediately below the base is an area of extensive fibrous tissue proliferation. A few eosinophils are noted. In the region of the ulcer the mucosa is absent. Sections through the remaining portion of the gall bladder reveal a slight diffuse eosinophilic infiltration with marked fibrous tissue proliferation.

DISCUSSION

Lesions of this type may occur more commonly than statistics would indicate. There is no apparent way of making a clinical diagnosis in the uncomplicated case. The definite demonstration of the lesion by X-ray would depend upon a chain of fortuitous circumstances. In the present case there was no concentration of the dye in the gall bladder. The etiological factors are also obscure. It seems unlikely that the single small stone is significant in this regard. If any analogy can be drawn from ulcers elsewhere in the gastro-intestinal tract this type of lesion is probably unimportant as a precancerous process. It is noteworthy, however, because of the non neoplastic complications detailed above which may follow its appearance.

CONCLUSION

A case of discrete benign ulcer of the gall bladder of obscure etiology is presented.

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A Case of Peptic Esophagitis

By

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and

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BENIGN ulceration of the esophagus is rarely diagnosed because the clinical picture is not well defined; it usually produces no definite Roentgen-ray findings, and esophagoscopy examinations are not often made. The following case demonstrates the diagnostic difficulties seen in these cases, throws some light on etiology, and presents therapeutic problems which are as yet unsolved.

The patient, the wife of a physician, was aged 56 when first seen in November, 1934. She gave a life long story of intermittent indigestion of a vague type, the trouble gradually growing worse during the past two or three years. At one time a diagnosis of gastric ulcer had been made after an X-ray examination, and she was known to have diverticulosis of the colon. In addition there had been sick headaches associated with the gastric complaint.

In spite of the fact that her complaint in recent years had been of difficult and painful swallowing, several roentgenologists had carefully examined her stomach and intestines without ever looking at the esophagus until in August, 1934, at which time an X-ray examination disclosed obstruction of the lower portion of the esophagus. Esophagoscopy examination proved this to be due to an annular ulcer two inches above the cardia. The tissue removed by biopsy was diagnosed as inflammatory by two different laboratories.

At the time we first saw the patient, she was suffering intense paroxysms of pain following attempts to swallow either solids or liquids. The pain usually lasted from several hours to eighteen hours and was so intense that morphine was often given though with little benefit. At times chloroform anesthesia had been induced to give relief. The difficulty was intermittent, the severe paroxysms occurring about once a day. A bismuth and phenol mixture had helped to prevent pain and had enabled her to take sufficient liquids to avoid dehydration. Under the fluoroscope, the upper three-fourths of the esophagus was seen to be dilated. About two and one-half inches above the cardia there was a smooth, tight stricture which looked as though a string had been tied around the esophagus at this point. After a few minutes the barium mixture began to seep through the stricture, outlining a seemingly normal lower esophagus. Examination of the stomach showed many reverse peristaltic waves, rippling up over the stomach and carrying barium back up the esophagus as far as the point of stricture. An hour glass constriction was present in the lower one-third of the stomach, but no indication of ulceration was made out. Administration of three-eighths grain of ephedrine hypodermically caused a perceptible relaxation of the esophageal stricture and relief of pain.

For a few days, the patient seemed to derive considerable benefit from treatment consisting of three-eighths grain ephedrine and three-fourths grain amytal three times a day, alkaline powders and frequent bland feedings. Mucin was used at bed time with the idea of providing a coating for the ulcerated area.

Symptoms again became aggravated after a short time. Esophagoscopy examination was then made under general anesthesia. The dilated upper esophagus was found to contain a large amount of food debris, although food had been withheld for more than twenty-four hours. The mucosa was boggy with edema, just as one commonly sees it in cases of stasis due to malignant stricture. The area of stricture itself was seen to be ulcerated and bleeding. Several pieces of tissue were removed for examination and the whole area painted with silver nitrate. It was impossible to pass the dilator through the stricture. The specimens were examined at Mayo Clinic and found to be inflammatory tissue.

Following this, there was improvement for several weeks. One month later it was possible to pass an esophagoscope through the stricture and the annular ulceration was discovered to extend from the stricture practically down to the cardia. Relief of stasis had permitted the mucous membrane of the upper esophagus to return to a normal condition. Under the fluoroscope, spasm appeared to be much less marked but there was still considerable narrowing.

After a short interval of improvement, difficulty in swallowing again became aggravated. Larostidan therapy was tried. The drug was given intramuscularly in dosage of 5 c.c. on alternate days for six doses but there was no improvement and the treatment was discontinued.

Since the patient was now becoming dehydrated and she was unwilling to tolerate wearing a nasal tube for feeding, gastrostomy was performed on February 19, 1936, with the idea of subsequently being able to carry out retrograde dilation of the stricture. Exploration revealed no involvement around the cardia and no evidence of an infiltrating growth.

A formula was prepared consisting of milk, cream, egg, Karo syrup, yeast, cod liver oil, liver extract, pureed vegetables, and orange juice, and this mixture was administered through the gastrostomy at hourly intervals. The gastric content was tested before each feeding and sufficient alkali was given to entirely neutralize any free acid which appeared. Paroxysmal pain, however, still continued to occur and was associated with the regurgitation of food into the esophagus from which it was often vomited. Prompt relief of pain followed vomiting food or emptying the

stomach by aspiration. It was soon found that orange juice induced an attack of pain but no other ingredient of the formula could be incriminated.

Subsequently the stricture was dilated at weekly or bi-weekly intervals up to a size 40 French dilator. There was never complete freedom from the difficulty in swallowing, but after a few months, the gastrostomy was allowed to close.

In September, 1936, a cycle of migrainous headaches began and concomitantly there was increased trouble in the esophagus. Subsequently it was discovered that she had become allergic to eggs and milk. After the omission of these foods, her headaches and pain were relieved and the paroxysms were lessened.

Our interpretation of the sequence of events in this case is as follows:

The woman was an allergic individual with definite sensitization to milk, eggs, oranges, and possibly other foods. On ingesting these foods, she developed a functional disturbance of the gastro-intestinal tract, and as a part of this disturbance, she had reverse peristalsis in the stomach and up the esophagus as demonstrated repeatedly both under the fluoroscope and by observation during the time she was being fed through the gastrostomy. These waves carried acid gastric contents up into the esophagus where eventually a peptic esophagitis resulted. Spasm from irritation, together with narrowing from the scarring produced obstruction which became complete only when spasm was marked. Dilatation of the esophagus above the point of stricture resulted from the retention there of food and liquid. Stasis lead to edema and changes in the mucosa of the upper esophagus. The condition differs from the ulceration seen in cardiospasm in that the ulceration in this case lies distal, not proximal, to the obstruction.

In the treatment of this case, we have attempted to keep the organic stricture dilated and have tried futilely to keep the gastric contents neutralized in order to allow the ulceration to heal. The real need, however, is to stop the reverse peristalsis which is keeping the esophageal mucosa bathed with acid chyme and this has not been satisfactorily accomplished.

Jackson (1) reported twenty-one instances of ulcer in over 4000 cases subjected to esophagoscopy examination, an incidence of about 0.5%, and found scars of healed ulcers in an additional 1.7%. This incidence may be too low for esophagitis was found to be present in 7% of over 3000 cases which were examined at post mortem at the Mayo Clinic as reported by Butt and Vinson (2). Of these, 76.5% were acute and only 1.5% chronic lesions. They make the significant observation that 46% of all cases had vomited or had had gastric lavage prior to death. In other words there was evidence of retrograde flow of gastric content through the esophagus in about one-half of these cases with acute esophageal inflammation. Jackson also considers gastric reflux to be a characteristic of such cases.

There are many causes for back-flow into the esophagus; i. e. post-operative nausea, hour glass stomach, peptic ulceration of stomach or duodenum with pylorospasm, pyloric obstruction, etc. In our case, we believe the reflux was on an allergic basis.

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Preplacing *B. Coli* by *B. Paratyphosus B.* in Large Intestines in Guinea Pigs*

By

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THE purpose of the experiments was to determine if the normal *B. coli* flora of the large intestine of guinea pigs could be replaced by a pathogenic gram negative bacilli. All adult animals died from infections before the flora was altered, or they were definitely pathological due to acute infectious process and the presence of the pathologic bacteria was a part of this process. We were unable to adapt the *B. paratyphosus B.* strain used to the large intestines of adult guinea pigs.

Young guinea pigs, beginning with the first day after birth were fed living *B. paratyphosus B.* by mouth. Varying dosage was employed. It was found

that 0.05 c.c. of a twenty-four hour old broth culture of *B. paratyphosus B.* could be tolerated by these young animals. The suspension was administered in 0.1 c.c. saline by dropping on the back of the tongue and stimulating swallowing. A catheter introduced through the esophagus causes injury and systemic infections followed. Fourteen young guinea pigs were used for the catheter experiments in feeding 0.05 c.c. of a twenty-four hour old culture of *B. paratyphosus B.* Twelve died and the bacilli were cultured from internal organs (kidney, spleen, liver and heart's blood) after death.

Sixteen young guinea pigs were fed daily for forty-eight to sixty-three days with 0.05 c.c. *B. paratyphosus B.* by oral administration without using a catheter.

*Research Laboratories of the State Department of Public Health and the University of Illinois College of Medicine, Department of Bacteriology and Public Health.
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All of these survived. These animals grew in the normal manner; no evidence of infection was present at any time.

Fecal examination showed a gradual increase in the *B. paratyphosus* B. Bacteriological studies showed the *B. coli* to be present occasionally and then only one or two colonies. The *B. paratyphosus* B. was the predominant bacteria on Endo's media. This persisted for six months after termination of feeding in eleven of the sixteen animals. Five animals showed a gradual increase in the *B. coli* at the expense of the *B. paratyphosus* B. The latter was always present, but was not the predominant member on Endo plate cultures. No bacteriophage against *B. paratyphosus* B. could be isolated from the feces of these animals after repeated trials.

Blood was tested for agglutinins immediately after the feeding of the *B. paratyphosus* B. was stopped, and again four and six months later. Four animals gave positive agglutination titers—two in dilutions of 1:160 and two in dilutions of 1:80, all others remained negative.

We wished to see if these animals were protected against intraperitoneal injection of *B. paratyphosus*

B. One-half, one and two c.c. of a twenty-four hour old broth culture of B. paratyphosus B. were injected intraperitoneally into control animals. Two c.c. were lethal within forty-eight hours, half of those receiving one c.c. died within seventy-two hours, none receiving 0.5 c.c. died. The fifteen surviving guinea pigs, (one animal was accidentally killed) now approximately eight months old, were injected intraperitoneally, five in each set with 0.5, 1.0 and 2.0 c.c. of a twenty-four hour old broth culture. All died within three hours with evidence of hypersensitiveness. Some were clearly anaphylactic and died within a few minutes. This was an unforeseen and unexpected result and terminated our experiment.

B. paratyphosus B. fed to young guinea pigs in small doses daily for several weeks becomes a part of the large intestinal flora of these animals. This bacillus replaces to a great extent the *B. coli* in the feces. Only four of sixteen animals harboring *B. paratyphosus* B. as a part of their intestinal flora showed serum agglutinins against this antigen. All of these animals however, were hypersensitive to intraperitoneal injections of *B. paratyphosus* B.

The Nutritional Value of Soybeans

By

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NEWARK, DELAWARE

INTRODUCTION

SOYBEANS are one of the few basic food materials which have survived the severe test of milleniums on a large scale natural experiment, involving today nearly one-half of the world's population, and are endorsed by modern science as well.

In the Orient soybean curd (tofu) has been in daily use since times immemorial, and is called "the meat without the bones," as it serves as a food rich in protein.* Soybean curd is obtained from soybean milk** by the action (on heating) of a precipitating agent, such as the mother liquid obtained in the manufacture of salt from sea water, or of plaster of Paris (50). Fresh soybean curd contains in the average 8% protein, 3% fat, and 1.5% carbohydrates. Smoked soybean curd contains 17% protein, and frozen soybean curd up to 58% (50). The digestibility of fresh soybean curd is 95% for the protein and 99% for the carbohydrates (84).

It is believed by some individuals that soybean milk could be introduced into the daily diet of the American people, forgetting that the United States have a highly developed Dairy Industry, and that soybean milk does not suit the American palate. Soybean milk has received much attention in the medical profession where its use is being

recommended for medicinal purposes, a field which seems to be very promising† (28, 60, 63).

What is known in this country as "soybean milk powder" is mostly nothing but a finely ground soya flour, or a blend of some kind of powder made from soybeans with minerals, sugar or cereal, and cod liver oil. It is a dry mix, in which the "soybean powder" is in some instances a solvent extracted soya flour, and in others a soybean product of very poor taste, prepared by a "wet process," where ample rancidization had every chance to incur. Publications on "soybean milk" in infant nutrition in the American literature are actually dealing with "dry mixes" (38, 94, 95, 107) containing soybean flour. The nutritive properties of soybean-egg powder as a substitute for cow's milk in the infant dietary have been studied in China (112, 91, 92, 93).

COMPOSITION AND PROPERTIES

As an economic source of valuable and wholesome dietary elements the soybean probably has no peer. The recently published statement by the Food Research Division, U. S. Dept. of Agri. (9), reads as follows:

"Soybean flour is a concentrated, wholesome, nourishing, and economical food. It is rich in

in the stomach soybean milk gives a much finer flocculent precipitate than cow's milk. The ingestion of soybean milk results in a feeblor secretion of gastric juice, the period of secretion is also shorter. The period of stay in the stomach of the finely flocculent precipitate of the soybean milk is shorter than that of the casein-fat coagulum of cow's milk. The peristaltic motion of the stomach is less after the ingestion of soybean milk and more coordinated than in the case of cow's milk, as shown by X-ray investigation (114). According to other investigators (35) soybean milk curdles at a lower acidity than cow's milk. However, the same period of time is required for curdling.

†Chemist, Agricultural Experiment Station.

*The low basal metabolism of the orientals was to a certain extent attributed to their being vegetarians, and the basal metabolism was accepted as a measure of efficiency of a nation until recent studies showed the basal metabolism of the Maya Indians to be about five per cent above that of the white race (101).

**Soybean milk contains from 2.7% to 4.2% of protein, about 1.5% of fat, and 2% of carbohydrates. It is manufactured in the Orient in a way similar to our almond milk (50). The nutritive properties of soybean milk have been studied chiefly in China (111).
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protein, not only in quantity, but also in quality. It is rich in fat, in minerals and in most of the known vitamins. It is a cheap source of protein, fat, minerals and energy. It is alkaline in reaction."

The composition of soybeans is dependent on the variety as well as on climate and soil conditions. The oil content may fall below 14% or may reach over 21%, while the protein may range from 30% to 50%. The average composition of U. S. grown soybeans† is: Moisture, 8%; ash, 4.6%; fiber, 3.5%; protein, 40%; oil, 18.7% (9).

American grown soybeans* were found to contain a total of from 2% to 3.82% of phosphatides (calculated as lecithin) (55), the larger part of the total being cephalin, and the balance chiefly lecithin (82). Nearly two-thirds of the soya phosphatides are bound in the seed to the protein, presumably to its Arginine fraction (43). The soya phosphatides are also invariably bound to a di- or polysaccharide (44).

Soybeans contain up to 1.9 per cent of Phytin (25). The phytic acid, which is soluble in ethyl alcohol, may partly be responsible for the higher phosphatide figures as calculated from alcohol-extractable phosphorus. The principal distinguishing characteristics of soybean lecithins are the low proportion of saturated fatty acid containing a larger carbon chain than C_{18} , and the presence of linolenic acid (67). Cephalin from soybeans shows no marked difference from the one isolated from animal sources (67).

The presence of phosphatides in soybeans may have some special physiological value because phospholipoids are constituents of all the body cells, the nervous tissue being particularly rich in phosphatides.

Soybean oil contains the following acids: Linolenic, 2.2%; linoleic, 49.3%; oleic, 32.0%; palmitic, 6.5%; stearic, 4.2%; arachidic, 0.7%; lignoceric, 0.1% (11). The digestibility of soybean oil by man was shown to be from 95% to 100% for daily doses of 100 gms. (50). Soybean oil was shown to induce the organism of rats to an unusual amount of activity (89), which phenomenon may be explained by the peculiar electrical behavior of soybean oil as shown by the Dalliacqua test.**

The odor of the crude soybean oil is considered to be due to the presence of methyl-n-nonyl ketone (100).

Refined soybean oil compares favorably with other edible oils. Nearly 90% of the total soybean oil production of this country goes into the edible channel.

Refined soybean oil is deprived of the phosphatides as well as of vitamins A and E (45). Crude expeller oil as well as solvent extracted oil contain from 1% to 3% of phosphatides.

Solvent extracted soybean oil (by benzene) contains free sitosterol esters and sitosterol-d-glycosid. Commercial soybean phosphatides contain up to 2.8% of this glycosid (56).

The Nitrogen-free extract of the soybean consists of (108): Galactan, 4.86%; Pentosan, 4.91%; Organic Acids (as citric), 1.41%; Sucrose, 3.31%; Raffinose, 1.13%; starch, 0.50%; Dextrin, 3.14%; Waxes, color principles, tannins, etc. (by diff.), 8.60%. Immature

soybeans, as well as the easy cooking varieties contain a higher percentage of starch. According to a more recent analysis (65), shelled soybeans contain only traces of starch, no dextrin, 5.26% sucrose, no reducing soluble carbohydrates, 5.60% stachyose, 4.83% Arabin, 6.18% Galactan, and 1.63% Cellulose. Only the sucrose and one-fourth of the stachyose have to be considered as glucose forming substances.

For cooked soybeans, the utilization of carbohydrates by man is from 81.4% to 89.9% (81). Only one-half of this figure was recently obtained (3) on rats by investigators who used raw solvent extracted soybean meal from unshelled beans. This emphasizes the importance of cooking.

"The soybean is the richest in protein of all known foods except dried egg white. Even such concentrated animal foods as dried beef and cheese contain less protein than the average soybeans" (9). Nearly all of the protein matter of the soybean consists of a globulin "glycinin"† with which is associated a small amount of legumelin and proteose (87). The isoelectric point of glycinin is a pH of 5.0 (33). Glycinin is readily soluble in NaCl solutions, and is precipitated by dialysis or by dilution (86). When soybean meal is treated with water, upwards of 16% of glycinin is dissolved, but in this case the solution is doubtless due to the potassium phosphates contained in the seed (86).

During the process of commercial solvent extraction of soybeans by benzene the protein is denatured, presumably through deamination and hydration (43), and only a small part of it can be extracted by aqueous leachings (43). Treatment of the glycinin with NaOH solutions results in the splitting off of one-half of the Arginine (69) and the loss of nearly one-half of the cystine sulphur (in the form of H_2S) (85). One should therefore be cautious in interpreting the results of experiments on the nutritive value of "purified" soybean protein.

Glycinin contains: Glycine, 1.0%; Valine, 0.7%; Leucine, 8.5%; Proline, 3.8%; Phenylalanine, 3.9%; Tyrosine, 1.9%; Cystine,† 1.10%; Aspartic acid, 9.4%; Glutamic acid, 19.5%; Arginine, 8.10%; Histidine, 1.40%; Lysine, 9.1%; Tryptophane, 1.7%; Hydroxy-glutamic acid, 5.5% (87, 9). There exist marked differences in the cystine content of the glycinin from different varieties of soybeans. While the glycinin from the Illini variety contains only .74% of cystine, the glycinin from the Mammoth Yellow, the Virgini, the Haberlandt, the Manchou, and the Chiquita varieties contain .92, .95, .98, 1.45 and 1.46 per cent respectively (20).

The protein of the soybean was found to be adequate for promoting normal growth and "physiologically good"§ (22, 59, 88). The favorable findings were all obtained on cooked soybean protein, while raw soybean protein is of lower biological value (34), especially when it is fed with the hulls (80).

Numerous feedings experiments conducted in this country as well as abroad established beyond any doubt that for babies the soybean proteins are com-

†The Manchurian commercial soybeans contain an average of 8.5% moisture, 14% oil, 40% protein, 2% non-starch polysaccharides, and 1.5% ash (33).

‡The soybean meal (33) contains only about 16.45% of oil. The rest there was in the country about 6,000,000 acres under soybean cultivation.

**See also A. A. H. Smith: "Some chemical aspects of soybean oil" (March 1934, issue of "Oil and Soap").

†For its calculation from Nitrogen the factor 5.7 should be used instead of the customary 6.25.

‡The old assumption that glycinin contained sulfur in some complex other than cystine (85) was confirmed in more recent times by the discovery of 1.6% methionine in glycinin (91).

§Efficiency of soybean protein in cystine has been reported by some authors (76, 101). Recently it has been found that cystine or its equivalent may exist in the raw protein of the soybean in a form which is not available to the animal (35). It appears that heating the soybean causes the cystine fraction of the protein to become available (35).

parable to cow's milk proteins (91, 92, 93, 94, 95, 107, 112).

The digestibility of soybean protein in cooked beans fluctuates between 60% and 80%*, depending upon the thoroughness of cooking and the fineness of the particles (purec) (39, 50, 84).

Pepsin was found to have a higher digestive effect on glycinin as compared with soybean protein denatured by benzene extraction, while pancreatin showed a higher digestive power on the denatured protein (43). The protein of soybean milk is more rapidly hydrolyzed by pepsin than that of cow milk, the reverse is true with trypsin. When acted upon by both enzymes, the protein of cow milk is shown to be the more completely digested. The optimal pH values for the enzymic proteolysis of these two varieties of milk as substrates are almost identical. The protein of soybean milk and the protein of cow milk were found to have a digestibility of 84.9% and 86.6% respectively (4). The "apparent" coefficient of digestibility of soybean protein by white rats in "experimental" expeller oil meal amounted to 85% (34)** The digestibility of protein in "processed" edible soya flour is still higher.

As early as 1915 it was discovered by an American physician (98) that soybean flour is of great value for feeding children, is readily digested, and is particularly useful as a food in summer diarrheas. This was confirmed by German as well as French physicians (12, 71, 90, 114) who recorded that on a soybean diet the intestinal flora turns *Gram*-positive.

It was discovered in recent times that *Lactobacillus Acidophilus*, when grown in a medium prepared from soybeans (with the addition of Lacto-Dextrin), develops much more rapidly than in cow's milk, maturing in ten hours, about half the time required for cow's milk cultures. The individual bacteria are fully fifty per cent larger, and far more robust in appearance. The number of bacteria per c.c. exceeds the count of milk culture by fifty to one hundred per cent. Soy acidophilus cultures are also much longer lived, retaining their vitality for many weeks, and appear to preserve the natural characteristics of the organism, so that it more readily adopts itself to the anaerobic life in the human intestine† (60).

Curative experiments on rats rendered anemic on an exclusive diet of cow's milk demonstrate that soybeans are effective in the regeneration of hemoglobin (2). When in dogs blood plasma proteins are depleted by bleeding, plant and grain proteins are quite well utilized to form new plasma protein, but soybean meal

probably should be rated at the head of this list. It is utilized with unexpected promptness and favors the production of albumin in contrast to other plant proteins which distinctly favor globulin production. The potency ratio of soybean meal is between 5. and 7. which places it in a class with liver (74).

The soybean contains the following mineral constituents (29) (in per cent of dry substance): Potassium, 2.095%; Sodium, .380%; Calcium, .230%; Magnesium, .244%; Sulphur, .444%; Chlorine, .025%; Phosphorus, .649%.‡ Excess of total base over total acid = 31.24 c.c. of *n* solution (per 100 gms.). According to other authors, the excess base is as high as 37.89 c.c. (71), and even 42.00 (61).

It has been shown that while alkalization of a human being by the administration of sodium salts (bicarbonate or citrate) is followed by a retention of water amounting to about one kilo and greater perspiration during exercise, the alkalization by the corresponding potassium salts results in a one kilo loss of water by the body and a marked reduction in perspiration during exercise (24). The deficiency of the soybean ash in sodium and the large excess of potassium places the soybean in the latter class of alkalizing agents.

Recent experimental studies on humans showed that when the alkalization by a diet consisting of two-thirds of a pound of soya flour + milk + vegetables has begun one or two days before the test, the fatigue incurred in a well trained cyclist in 50 minutes as against a normal period of 36 minutes, and when the ergometer is set at a high resistance the period of fatigue inducement is extended to 33 minutes as against a normal of 19 minutes (24). Attempts to build up an adequate alkalosis by a liberal diet of potatoes, milk and other vegetables have failed (24).

Feeding soybeans to rabbits results in an increase in the inorganic phosphorus in the blood (42). The available figures of phosphorus and calcium metabolism in infants were obtained on solvent extraction soya flour, on which chemicals were acted upon during the process of manufacture, and to which minerals were added (107).

Of the enzymes, soybeans contain: Amylases and Diastases (17, 32, 108), Proteases§ (16). Lipases* (true lipases and esterases) (10, 51, 108), urease (110), uricase (79), oxidases and peroxidases (7, 50, 108). It has been recently reported (105) that while the lipase potency does not vary with the varieties of soybeans, the peroxidase varies from 7.56 to 88.02 units, and the urease from 26.86 to 60.76 units. The peroxidase of the soybean has found application in

*Higher figures were obtained where some soy sauce was used for seasoning the beans. Soy sauce is very popular in the Orient for use in cooking and as a relish or condiment to increase the flavor and palatability of the diet. In odor and taste it is not unlike a good quality of beef extract. It is prepared from a mixture of soybeans, wheat or barley, salt and water, by a long continued fermentation where *Aspergillus Orizae* plays a leading role, in co-operation with certain bacteria (84). Soy sauce contains an average of 19% NaCl, and from 1% to 8.5% of sugars (50). The cleavage products of soy sauce contain among other substances some histamine, to which is attributed the stimulating action of the sauce on the musculature of the stomach and intestines as well as an enhancing action on the absorption of foods by acting as a relaxing agent on the capillaries of the gastric and intestinal mucosa (11). It was also found that soy sauce contains substances which stimulate the saccharifying action of Taka-Diastase from 16 to 32 times, and the proteolytic action of pancreatine from 4 to 8 times (52). Soy sauce is therefore valuable as a seasoning agent and also as an ingredient of other table sauces (19); Worcestershire sauce consists of soy sauce, vinegar and spices.

**The temperatures given are lower than the ones actually used in commercial oil milling by the expeller method (6)

†The Soy Acidophilus milk, which the Dionne quintuplets take today, is given them to prevent the recurrence of the severe bowel infection which they suffered when four months old. They were relieved by the use of Soy Acidophilus milk after other measures had failed (62).

‡Whole soya flour contains: Total ash, 5.7%; Potassium, 1.860%; Sodium, .230%; Calcium, .300%; Magnesium, .380%; Phosphorus, .700%; Sulfur, .365%; Chlorine, .071% (9). According to another author (58) the P₂O₅ content amounts to 32.2% of the total ash. Soybeans contain 2 to 3 times as much ash as does wheat 4 times as much potassium and sodium, 5 times as much calcium 3 times as much magnesium 2 times as much phosphorus, about the same amount of sulfur, but only one-third as much chlorine. Soybeans are also richer than navy beans and lima beans in most mineral constituents (9). Soybeans contain appreciable amounts of iron and copper (2). It has been established that the iron in soybeans is "available" to over 60 per cent, being equal in this respect to beef and pork liver, superior to beef muscle, and twice superior to spinach and blood (95).

§Experimental feeding of raw soybeans (soaked over night in water) to rabbits resulted in some instances in lesions in the stomach which could be ascribed to the digestive effect of the proteolytic enzymes of the soybeans, as the organism possesses no corresponding antiferment (42).

*The soybean lipase from raw soybeans can be absorbed from the intestinal tract into the blood, and is capable of causing fat necrosis in animals (51).

the baking industry for the bleaching of dough (99, 113), and the urase for the leavening of bread in the presence of urea.

As early as 1917 it has been found that soybeans contained an adequate amount of the "water-soluble vitamin" and contained also "some of the essential fat-soluble vitamin" (antirachitic as well as anti-xerophthalmic) (88), which findings were corroborated in the same year by others (23). A recent quantitative estimation showed that soybeans contained three times as much B₁ but only two-thirds as much B₂ as does dried cow's milk (103). In 1925 it was demonstrated that a daily dose of one c.c. of solvent extracted soybean oil was sufficient to prevent as well as to cure rickets and xerophthalmia in young growing rats** (40). It is reported that there are higher concentrations of Vitamin A and B in the soybean embryo than in the endosperm (83). There is also no doubt that the Vitamin A content of the soybeans varies, depending upon the variety of the soybean and the degree of maturity. In 1925 the presence of Vitamin E in soybeans was established (22), which findings were confirmed recently by other investigators† (109).

In 1930 the discovery was reported that soybean feeding has an enhancing effect on the clotting of hen's blood (41). Later investigations (1935) showed it to be related to the oil fraction of certain seeds, and the term "Antihæmorrhagic Vitamin K" was proposed for the active principle (21). The addition of 2 per cent of soybean oil to an experimental diet provides an adequate level of Vitamin K for newly hatched chicks (53).

In 1936 a protective factor against nutritional encephalomalacia of chicks was discovered in the non-saponifiable fraction of certain edible oils, which are headed by soybean oil (31).

NUTRITIVE VALUE

In 1934 the nutritive value of green immature soybeans has been studied, and the following conclusions reached (75):

"As compared with most vegetables, they have unusually large amounts of protein, fat, calcium, phosphorus, and iron. Cooked immature soybeans proved to be a very good source of vitamins A, B and G, and a poor source of vitamin C."

Studies of one month duration on four human indi-

viduals kept on a mixed diet containing substantial quantities of boiled mature soybeans showed that the protein, fat and carbohydrates of the soybean were assimilated to an extent of 88%, 88% and 100% respectively as compared with those of meat and fish (70).

It has been established that the longevity of rats on a diet of ground raw soybeans is much shorter than on whole raw soybeans (13). This phenomenon is due to the rapid incurrence of rancidity in the crushed raw soybeans, enhanced by the peroxidase of the soybean seed, resulting in the destruction of vitamin A and E, and in the formation of toxic oxidation products from the oil, such as nonylaldehyde and dioxiacetone‡ (45, 106). Treatment with "active" ground soybeans destroys at least 99 per cent of the vitamin A present in cod liver oil (30), and the incorporation of the latter in feeds will therefore be rather harmful than beneficial (68). The destruction of vitamin A and the formation of toxic substances in feeds containing either ground raw soybeans or rancid soybean meal§ were greatly responsible for most of the poor results obtained which cast an undeserved shadow on the quality of soybean protein, on the vitamin A content of the bean, or on the calcium content of the soybean ash.

It is also necessary to take in consideration the fact that, in spite of being rich in calcium (0.25%),* the soybean contains an excess of fat over a favorable Ca/Fat ratio (48), and the diet has to be balanced accordingly.** Yet, some investigators who believed the soybean to be deficient in minerals were adding from 20 to 25% of butter fat to an experimental diet containing soybeans, and, of course, they had to counterbalance the ill effect of excess fat by the addition of 5 per cent of artificial salt mixture (88).

In order to prepare a soya flour of satisfactory keeping quality which is suitable for human consumption, it is essential to inactivate the peroxidases, oxidases and lipases of the soybean by an appropriate heat treatment (49), which also causes the methyl-nonyl ketone (100) to volatilize, leaving a flour of pleasant taste. Average data on three types of flour (of which only the high fat flours are actually "processed") are as follows (9): See Table on page 181.

One pound of processed whole soya flour (from shelled beans) has a fuel value of from 1980 to 2070 Calories (65).

In a recent authoritative publication† it is stated that "Soybeans and soybean flour may properly be considered as having protective food qualities, because they are rich in minerals, rich in high quality protein, rich in fat, and rich in vitamins, and hence serious thought should be given to their inclusion in the American diet."

*On the other hand there are experimental data (54) showing that soybeans have comparatively little Vitamin D value. The high phosphorus content of the soybeans, the large part of which is composed of phytates, might have been responsible in some instances in simulating Vitamin D action (115, 131). Attempts were made to correct the deficiency of various soybean flours in Vitamin D (in solvent extracted flour in Vitamin A as well) in baby foods through the incorporation of cod liver oil or egg yolk. The use of cod liver oil in blends with soya flour should be discouraged as the oil is subject to rapid rancidity in view of the large surface exposed to oxidation in the surface of the flour particles, resulting in the destruction of Vitamin A, D and E, in the formation of toxic aldehydes and ketones and in a rancid taste. (Such practice also encourages the use of inferior grades soya flour since its poor taste is veiled by the cod liver oil). Egg yolk is also subject to deterioration in blends with soya flour, and it adds, unnecessarily, oil and phosphates to soya flour which is already rich in these substances.

†An edible soybean oil, containing Vitamins A and E, as well as the phosphatides, can be prepared from refined edible whole soya flour (45). With the addition of irradiated ergosterol, such Vitamin D enriched soybean oil could be incorporated in our daily ration, and this action in many instances the necessity of having recourse to cod liver oil. While for human beings cod liver oil is fatal in large quantities, and cod liver is best avoided in animals, cod liver oil causes paralysis (due to degeneration of skeletal muscles, and incomplete atrophy of the heart muscle) on a synthetic diet containing cod liver oil (72).

‡Experiments showed that while young growing rats are capable of subsisting for 30 days without any vitamin A in the diet, they die in 8 days if given butter oxidized by exposure to ultraviolet rays, with the formation of peroxides and all the resulting oxidation products (106). The irradiation of milk and bread by ultraviolet rays should therefore be discouraged.

§The particles in hydraulic press and expeller meal have the disadvantage of being coated with an oil film which offers a large surface to oxidation.

¶Confirmed by feeding experiments on animals (44).

**Even a large amount of cod liver oil in a ration produces an entirely atrophic effect (74).

†By the Food Research Division, Bureau of Chemistry and Soils, U. S. Dept. of Agriculture (9).

Since the ash of the soybean is strongly alkaline† the incorporation of soya flour into a mixed diet counterbalances its acid components. On an alkaline diet the organism is spared the necessity of providing ammonia to neutralize the inorganic acids obtained

	High fat flours %	Press cake flours %	Solvent extracted flour*
Moisture	7.04	7.70	7.73
Ash	4.60	5.75	2.66
Fat	21.11	7.30	1.58
Fiber	2.30	3.03	3.04
Protein	41.55	47.45	68.74
5% K ₂ SO ₄ soluble N** (% of total N)	25.20	35.00	8.90
1% NaCl soluble N** (% of total N)	21.60	26.50	7.00
CaO***	0.28	0.35	0.61
P ₂ O ₅	1.21	1.40	1.03
Phosphatides (as Lecithin)****	1.10	1.30	0.66
Alkalinity*****	24.10	30.20	8.80
Urease activity*****	2.50	2.40	0.30

*On one commercial sample which it seems was subjected during the process of manufacture to treatment with chemicals

**Flours prepared from roasted beans as well as from beans that had been dipped in hot oil are especially low in K₂SO₄-soluble protein and in NaCl soluble protein

***Soybean flour is rich in Calcium (9) 'It is quite evident that soybean flour is one of the cheapest sources of Calcium' (9)

****One pound of soybean flour contains therefore as much lecithin as 4 to 6 eggs" (9)

*****C of N acid per 100 g sample

*****C of N/10 ammonia

from the food (37). Fundamental studies on "Protein Requirement and Mineral Metabolism," which were published in 1931 (14), established the following facts:

1. That the utilization of the food proteins depends, directly or indirectly, from the ratio inorganic bases/inorganic acids in the organism as well as in the food;
2. That a big excess of bases in the organism as well as in the food is a necessary precondition for an optimal utilization of protein;
3. That, therefore, a real minimum for protein requirement can be found only when there exists an excess of bases in the organism as well as in the food;
4. That with the increase of the excess of acids in the food as well as in the organism itself the nitrogen requirement of the organism mounts uninterruptedly until finally the physiological

impossibility of an immediate excretion of the by-products through the kidneys prevents a further rise and produces the illusion of a storage;

5. That in this way it is possible for the optimal figures of Voit to become under certain conditions the minimum figures.

The conclusion to be drawn from these findings is that the alkalinity of the soybean ash is a highly important factor for causing a saving in protein, and this is probably the main part of the explanation why experimental data showed that a human organism is able to store three times as much Nitrogen from a soybean food as from meat§ (96).

Soya flour does not act as a strong stimulant for gastric acidity, but is rather acid reducing, does not overburden the stomach, and does not affect the normal course of gastric motility. The digestion of soya protein goes remarkably rapidly, and the soya meal leaves the stomach mostly in 2½ to 3 hours, and in some instances even in 80 minutes (81).

The therapeutic uses of soybean preparations have been studied mostly in Germany (18, 114).

Soybean flour in any proportion up to 30% can be used with flour, white or whole wheat, not only for making bread but also for cake and other baked products. Bread made with 20% whole soya flour and 80% white flour contains a somewhat higher percentage of water and about 150% more ash and 40% more protein than white bread* (9).

Experiments conducted in 1921 by the U. S. Department of Agriculture (57) showed that bread made with a mixture of 25 parts of soybean flour and 75 parts of wheat flour contained a protein mixture and water soluble vitamins adequate for normal growth. A similar bread containing 15 parts of soybean flour and 85 parts of wheat flour likewise furnished adequate proteins and water soluble vitamins for normal growth. These mixtures of the soybean and wheat protein were found two or three times more efficient than the proteins from wheat alone. The results obtained by other authors (53) in Japan, when 10% soya flour was used to supplement corn or rice, were also good. In 1931 experimental studies conducted in Poland on the effect of soya—wheat and soya—rye bread on growth lead to the conclusion that a supplementary relation exists between the proteins of white wheat flour, or rye flour and soybean flour** (64).

In 1927, in Italy, studies on the nutritive value of a sole diet of soya bread† were conducted on six normal individuals, who received soya bread for periods of from 4 to 6 days (26). The average daily ration was 739 gms. of a 10% soya bread per capita, with a protein content of 97.3 gms., and 2,940 Calories. Two other normal individuals received for a period of five days a sole diet consisting of 831.5 gms. of a 20%

†The acidity or alkalinity of foods (in c.c. of N acid or alkali per one oz.) is (61):

Whole milk	0.5 (alk)
Soybean	12.0 (alk)
Wheat flour (pat)	2.7 (ac)
Bread (white)	2.0 (ac)
Beefsteak	3.0 (ac)
Eggs	3.1 (ac)

The high alkalinity of whole soya flour has made it a very effective remedy in the treatment of pyrexia in children, in eczema, and diabetes (12, 71). In cases of eczema due to idiosyncrasy to milk of animal origin soya flour has a double therapeutic value due to its high alkalinity coupled with the presence of glycine instead of the casein and lactalbumin.

§Performed on two individuals one given the meat and the other the soya diet

**A well baked soybean bread possesses an attractive crust a rich cream-yellow crumb, and has an agreeable aroma and taste. In other words it has appetite-appeal" (9).

†Some investigators explain this phenomenon mainly by the supplementary action of the soybean lysine and arginine on wheat flour

‡Baked from military whole wheat flour to which were added 10% or 20% of solvent extracted soybean flour. The shortage of fat was supplemented by giving with the bread from 25 to 30 gm. of butter per day

soya bread, containing 127.6 gms. of protein, and 3,273 Calories per capita per day. The utilization of the soya bread was:

	Total absorption from the 10% soya bread %	Total absorption from the 20% soya bread %
Dry substance	93.72	92.41
Calories	93.84	92.43
Nitrogenous substances	83.40	80.30
Fat	94.13	93.70
Carbohydrates	96.59	97.01
Mineral substances	68.60	62.53

While the assimilation of the 20% soya bread lies within the satisfactory limits for white bread, the 10% soya bread was found in appearance, digestibility and utilization equal to a bread from sole wheat of best quality, having the advantage of containing a higher percentage of nitrogenous substances (26). The general conclusions were that the soybean flour, when added to bread or other nutritive food preparations, is going to become a valuable supply of cheap protein for the alimentation of the people (26).

In 1928 complete metabolic experiments were conducted in Germany on ten normal individuals on the utilization of a sole diet of a 20% soybean bread* (from solvent extracted as well as from whole soya flour) with the following results (80):

	Utilization (In per cent)				
	Nitrogen	Carb.	Fiber	Ash	Calories
Bread containing 20% of solvent extracted soya flour	79.61	95.91	51.93	67.94	91.75
Bread containing 20% of processed whole soya flour†	80.40	98.58	55.22	76.07	94.06

The utilization of carbohydrates in 20% whole soya flour bread is superior even to the utilization of starch in white bread (80).

In 1927 another important metabolic experiment was conducted in Germany for five days on one individual who received a sole diet of 900 gms. of soya-rye bread* (containing 15.9% protein) plus coffee and butter (97). The results showed that the incorporated soya protein was extremely well digested (93%), did not cause any disturbances and was chiefly utilized for building and improving the body of the experi-

mental person, and the minerals were also, as normally, stored up in the body in corresponding amounts. The soya-rye bread did not show any irritating properties, and rather a lessening of these on the intestines as compared with rye bread. The addition of soya protein acted as if some animal protein was added. In five days the man gained 11.09 gms. of Nitrogen, corresponding to 69.41 gms. of protein or about 352 gms. of muscular meat. Besides, the soya protein did not produce any undesirable rise in the activity of the intestinal glands, which is a noticeable advantage. The authoritative conclusions of the experimenter were that the introduction of such a soya bread for human consumption should be recommended "since the enriched bread is excellent in its exterior, taste and utilization, since it keeps fresh for an extraordinary long time, and since the added soya protein is much better utilized than the proteins of the usual cereals" (97). The incorporation of soya flour in bread may help the baking industry in our country to recover the 20% decline in wheat consumption which occurred since 1904 (47).

Besides bread and bakery products** the other main outlets for soya flour are for the manufacture of crackers†, pancake flour, cocoa-malt mixest, baby foods, chocolate, puddings, ice cream powders, macaroni products, and sausages.§ The addition of soya flour renders these products more nutritious and palatable* (46, 49). The incorporation of over 3 per cent of soya flour into sausages is prevented in this country by the lack of a simple and accurate method for the determination of the percentage of soya flour for Governmental control purposes (66).

CONCLUSIONS

The 1935 recommendations of the Committee on Nutrition of the League of Nations emphasize that all possible steps should be taken to make food supplies, and especially protective foods, available at prices within the reach of all classes of the community. One answer to this recommendation is given in a recent publication from the Food Research Division of the U. S. Dept. of Agriculture (9), which reads as follows:

"The most expensive food constituents are minerals, vitamins, proteins, and fats. Soybean flour is rich in all these food constituents and yet relatively cheap. The moderate cost of soybean flour makes it possible for people of small incomes to obtain the maximum of these essential nutritional constituents required by the body which in the form of other foods might be beyond their reach."

*Such as coffee cake and doughnuts.

†Only solvent extracted soya flour gives a product that will keep indefinitely.

‡The cocoa-malt blend often sells a soya flour of poor quality.

§Mostly meat flours are being used today for sausages. Since sausages containing a substantial amount of soya flour can be sold at a reduced price, this may provide the packing industry of our country with a means of expanding the consumption of meat.

*Soya flour has also been recommended as an emulsifier for mayonnaise (27), and recently the whipping ability of soybean protein has been discovered (71).

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220 parts of soya flour, 48 parts rye flour, and 32 parts wheat flour.

†From shelled beans. Experiments showed that the presence of hulls in soya flour reduces the longevity of white rats by 20 per cent.

*From soya flour extracted by a benzene-alcohol mixture.

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Blood Diastase in Hepatic and Biliary Disease*

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ALTHOUGH the pancreas is held to be the chief site of formation of diastase it has been noted that after pancreatectomy a certain amount of diastase still remains in the blood, and has a definite tendency to return to normal levels (1, 2). Very small amounts also continue to appear in the urine. Consequently it is assumed that diastase may have its origin in other organs than the pancreas, particularly in the liver.

Whereas the diastase estimation in blood and urine has been widely accepted as useful means for investigation of pancreatic function, the fluctuations of this ferment in disorders of the liver are hardly known. In a brief publication, Somogyi (3) recently devised a new method for the determination of diastase in the blood, in which he reports that low values are found in patients with liver damage. The amount of sugar in the serum is determined, then 1 c.c. of serum is incubated for 30 minutes at 40° C. temperature with ordinary freshly prepared potato starch, sugar is again determined, and the difference between the first and second determination gives the activity of diastase present in the serum. Thus the quantity of the

tory results and enables quantitative evaluation of diastase. According to Somogyi and our own experience, this method is sufficiently sensitive to permit the determination of very small quantities and fluctuations in the amount of enzyme. The values obtained by us in normal fasting individuals and animals correspond to those found by Somogyi. They vary ordinarily between 80 and 100, as shown in Table I, which gives the results obtained in 15 normal individuals. The figures demonstrate that there is no parallelism between the blood sugar and diastase level.

Forty patients suffering from various liver diseases, 32 of them associated with jaundice, were examined. In some of them the diastase determinations have been repeated several times during the course of the illness. The total number of diastase estimations in this group amounts to 67. In many instances the bilirubin content of the blood has also been determined, as well as the diastase output in the urine, made by the Wohlge-muth method. The results are given in Tables II-VI. In 12 patients the blood diastase was found within normal limits, the rest (28 patients) showed a definite lowering, which we consider below 70. In the majority the blood diastase was much lower—less than 50.

The diminution of diastase did not parallel the blood sugar, which remained within the normal range in most instances; it also did not correspond to the severity of the jaundice at the onset of the disease. However, we could observe a gradual increase of the blood diastase together with the clinical improvement. Patient No. 4 (Table VI) may serve as an illustration of this observation. He was suffering from dermatitis exfoliativa, lasting several months with clinical signs of liver involvement, and a markedly enlarged liver. Three successive determinations at different intervals revealed complete absence of diastase in the blood. At this period the galactose test showed a slightly increased excretion of galactose in the urine (4.25 g.) and a negative Takata-Ara reaction of the serum. There was no jaundice during the entire period of illness. With the improvement of the dermatological and general condition, the blood diastase rose first to 22 and later to 43. A similar, but less severe case (No. 7, Table VI) also showed at first a marked lowering of diastase (29) which increased to 48 after clinical improvement began. The same was found in patients suffering from catarrhal jaundice who showed at the onset a lowering of blood diastase (Table II). In the instances of catarrhal jaundice with normal diastase values (Nos. 2, 5, 8, 11, 12, 14) the disease had a milder course and was of short duration. On the other hand, a gradual lowering of the value was observed in patients in whom a further aggravation of the disease had taken place. This group contains only two instances where the diastase was above normal, including case No. 2, Table III, who was suffering from repeated attacks of cholecystitis and cholangitis, with

TABLE I
Blood diastase in normal people

No.	Patient	Blood sugar in mg. per 100 c.c.	Blood diastase in m.u. % of sugar (Somogyi method)
1	P. E.	—	110
2	Sb. A.	—	95
3	Ch. J.	—	160
4	B. Z.	—	68
5	M. H.	94	110
6	S. B.	99	160
7	I. A.	75	79
8	M. I.	92	97
9	M. B.	94	97
10	Sb. S.	92	164
11	E. B.	—	71
12	N. P.	125	110
13	B. E.	60	59
14	M. L.	87	102
15	J. G.	114	76

enzyme is expressed as the amount of reducing matter, in terms of glucose, which is produced by a known amount of the enzyme-bearing material under standardized conditions. This method gives satisfac-

*From the Medical and Outpatient Departments and Chemical Laboratory, Rothschild Memorial Hospital, Jerusalem, July 27, 1937.

TABLE II
Blood diastase in catarrhal jaundice

No.	Patient	Date	Blood sugar in mg. %	Blood diastase	Blood bilirubin in mg. %	Remarks
1	M. F.	July 3rd, 1935 July 18th, 1935	92 84	42 108	2.9 —	Takata-Ara positive Improving
2	J. A.	Aug. 23rd, 1935	85	80	2.6	
3	G. A.	Aug. 23rd, 1935	120	40	1.0	
4	E. S.	Sept. 9th, 1935 Oct. 2nd, 1935 Oct. 10th, 1935	122 111 117	42 97 93	6.8	Takata-Ara negative Improving
5	Sh. Sh.	Oct. 13th, 1935	109	76	0.5	
6	Ch. R.	Nov. 14th, 1935	79	44	3.6	
7	E. P.	Nov. 28th, 1935	81	59	0.8	
8	R. S.	Nov. 27th, 1935 Jan. 1st, 1936	133 89	71 111	1.6	Improved
9	D. E.	Jan. 1st, 1936 Jan. 31st, 1936	98 90	40 72	1.65	Improving
10	E. R.	March 23rd, 1936	100	60	1.8	
11	L. M.	Aug. 16th, 1936 Aug. 25th, 1936	100 77	91 176		Urine diastase—5060 units Urine diastase—40 units
12	P. S.	Nov. 17th, 1936	89	99	0.78	Urine diastase—40 units
13	S. G.	Nov. 27th, 1936	81	52	1.86	Urine diastase—640 units
14	E. E.	Jan. 4th, 1937	114	86	0.86	Urine diastase—40 units
16	Sh. H.	March 11th, 1937 March 10th, 1937 March 22nd, 1937 March 26th, 1937	108 100 100 80	48 256 180 92	2.36	Acute pancreatitis Urine diastase—160 units Urine diastase—50 units

jaundice, accompanied by fever. There was also a persistent steatorrhea, glossitis and a hyperchromic anemia, i.e. the symptom complex of sprue. At the onset of his illness (April 3, 1935) the blood diastase was normal (105). On September 15, 1935, when the above mentioned symptoms were more pronounced, the blood diastase was definitely raised (180), while the urine diastase was still normal (40 units). The second patient (No. 15, Table II) was admitted to the hospital with acute catarrhal jaundice. He complained of abdominal pain which was clinically and roentgenologically proved to be due to an old duodenal ulcer. While under observation, the pain became more intense and radiated to the back, fat was found in the stool, thus indicating involvement of the pancreas. The blood diastase which was first below normal (48)

rose suddenly to 256, subsequently dropped to 180 and then, with subsiding signs of pancreatitis, to 92. The increase of the diastase level in the blood, in spite of long standing liver injury, we ascribe to the pancreatic dysfunction, and the blood diastase in these two cases was the result of two conditions which influence the diastase level in an antagonistic manner. This question will be discussed later. In the six cases of atrophic cirrhosis of the liver (Table IV), three had normal diastase value (Nos. 1, 5, 6); one (No. 3) slightly reduced, and the other two (Nos. 2, 4) showed a marked lowering of the diastase with progress of the disease. The functions of the liver tend to remain normal in the type of hepatic disease exemplified by atrophic portal cirrhosis of which the pathological evolution is slow. The deviations are present when superimposed

TABLE III
Blood diastase in cholangitis with jaundice

No.	Patient	Date	Blood sugar in mg. %	Blood diastase	Blood bilirubin in mg. %	Remarks
1	S. R.	April 2nd, 1935	—	25	—	Carcinoma of the pancreas
2	Sh. C.	April 3rd, 1935 Sept. 15th, 1935	— 120	105 180	— —	Sprue Urine diastase—40 units
3	I. P.	July 23rd, 1935	100	51	1.16	
4	S. R.	Dec. 6th, 1935	78	53	0.8	
5	A. Sh.	June 12th, 1936 June 18th, 1936	79 82	58 30	0.5	Carcinoma of the pancreas
6	A. I.	July 27th, 1936 Aug. 14th, 1936 (after Cholecysto- gastrostomy)	153 136	17 52	4.6	Urine diastase—160 units Urine diastase—5120 units

TABLE IV
Blood diastase in cirrhosis of the liver

No.	Patient	Date	Blood sugar in mg. %	Blood diastase	Blood bilirubin in mg. %	Remarks
1	M. Z.	Oct. 27th, 1935	86	92	0.5	
2	Ch. B.	Nov. 26th, 1935	120	32	1.4	
		Nov. 6th, 1935	154	25	1.45	
3	R. M.	March 20th, 1935	129	61	—	
4	B. B.	Aug. 10th, 1935	116	92	0.5	
		Jan. 1st, 1937	100	84	—	
		March 5th, 1937	84	32	—	Takata-Ara positive
5	E. Z.	Nov. 27th, 1935	104	79	0.8	
6	I. C.	May 6th, 1937	76	141	—	Takata-Ara positive

TABLE V
Blood diastase in post dysenteric hepatitis

No.	Patient	Date	Blood sugar in mg. %	Blood diastase	Urine diastase in units
1	M. M.	April 29th, 1935	125	22	—
2	L. L.	May 14th, 1935	97	36	—
3	F. B.	July 25th, 1935	59	53	—
4	Ch. B.	Nov. 24th, 1935	102	58	20
5	G. B.	Nov. 27th, 1935	109	59	320
6	A. Sh.	Nov. 27th, 1935	121	49	160

hepatitis or terminal cholemia occurs. Accordingly, the blood diastase showed no variations from normal in the cases in which jaundice was absent and in which the mechanical obstruction of the portal circulation produced the outstanding symptoms. This agrees with the findings of the cholesterol partition of the blood obtained by E. Z. Epstein and E. B. Greenspan (4).

The following group comprises 26 patients suffer-

ing from various affections of the gall bladder (Tables VII and VIII). There were among them 7 patients with acute cholecystitis (Table VII). All of them except one had a normal diastase in the blood. The one with the low diastase level (No. 6) was a pregnant woman who was suffering from acute cholecystitis. Two successive determinations revealed practically the same result (36 and 32). The complicating pregnancy may account in this instance for the low blood diastase. Another patient (No. 2) showed at the onset of the acute cholecystitis a slight lowering of the blood diastase (58) which became at once normal (135) when the attack subsided. Of the 19 patients with chronic gall bladder disease (Table VIII) only 4 had normal diastase, the rest of them showed a definite lowering. Two patients with chronic inflammation of the colon accompanying the cholecystitis (Nos. 2 and 4) had the lowest figures. In the case of No. 2 an acute exacerbation of the colitis accompanied by fever caused a drop of diastase to 24 which rose gradually to 62 and 103 with the patient's improvement and the remission of the colitis.

As far as the presented data in non-obstructive biliary disease permit, we can assume that acute dis-

TABLE VI
Blood diastase in a miscellaneous group of liver disorders

No.	Patient	Diagnosis	Date	Blood sugar in mg. %	Blood diastase	Blood bilirubin in mg. %	Remarks
1	M. K.	Hepatosplenomegaly, Icterus	April 2nd, 1935 Oct. 10th, 1935 March 20th, 1936	— 129 105	45 57 51	— 0.53 1.4	Patient's condition becoming worse
2	I. S.	Malaria with Icterus	May 9th, 1935	89	44	—	
3	P. L.	Acute nephritis with subicterus	May 26th, 1935 June 2nd, 1935 June 15th, 1935 June 23rd, 1935	70 70 84 84	33 49 71 77	— 0.74 — —	Improving
4	S. I.	Dermatitis exfoliativa, Hepatitis	June 11th, 1935 June 12th, 1935 July 7th, 1935 Dec. 17th, 1935 Feb. 16th, 1936	123 110 79 — 110	0 0 0 22 43	— — — — —	Takata-Ara negative, Galactose in urine 4.25 g. Improving
5	K. L.	Malaria with Icterus	Dec. 6th, 1935 Dec. 8th, 1935	75 50	109 62	— —	Jaundice increasing
6	D. A.	Hepatosplenomegaly, Subicterus	Dec. 20th, 1935	109	71	1.5	
7	I. W.	Dermatitis exfoliativa, Hepatitis	Aug. 7th, 1935 Dec. 31st, 1935	112 107	29 44	0.5 —	Improving

TABLE VII
Blood diastase in acute cholecystitis

No.	Patient	Date	Blood sugar in mg. %	Blood diastase	Urine diastase in units	Remarks
1	L. K.	July 26th, 1935	70	100	—	Improving
2	R. K.	Sept. 11th, 1935 Sept. 28th, 1935	83 116	68 135	40 —	
3	M. R.	Sept. 21st, 1935	148	112	—	
4	R. N.	April 16th, 1936	104	95	40	
5	S. M.	Sept. 21st, 1936	110	70	50	Pregnancy
6	Sh. C.	Nov. 13th, 1936 Nov. 24th, 1936	104 98	36 32	160 40	
7	M. G.	Jan. 1st, 1937	106	102	—	

cases of the gall bladder have no effect on the liver, whereas chronic gall bladder disease produces a various degree of liver damage, manifested by lowering of the blood diastase in the majority of instances.

Of particular interest is a patient (R. Sh.—Table IX) suffering from repeated attacks of common duct stones and cholangitis in whom the blood and urine diastase fluctuations are particularly significant. The history of this patient is briefly as follows:

September, 1931. Cholecystectomy and removal of several stones after attacks of cholelithiasis, accompanied by fever and jaundice.

June, 1935. Second admission. For the last three weeks, pain in right upper quadrant radiating to the back and right shoulder. In the hospital frequent attacks of chills

and transient icterus. The blood diastase at the admission was normal, then with progressive symptoms and repeated attacks of cholangitis a tendency to become low.

September 1, 1935. Cholelithotomy. Four stones from the common duct removed.

September 9, 1935. After removal of the drain clay-colored stool, bile excreted through wound. Occlusion, probably inflammatory in origin, at the papilla Vateri is assumed.

September 16, 1935. A sudden rise of the blood diastase to 393 and 542—normal urine diastase.

September 18, 1935. Blood diastase normal (93). Large amounts (10,000 units) were found in the urine the same day and the following day. Gradually, however, the urinary diastase became normal.

January 1, 1936. Second cholelithotomy was performed, because of recurrent attacks of pain in the right upper

TABLE VIII
Blood diastase in chronic cholecystitis

No.	Patient	Date	Blood sugar in mg. %	Blood diastase	Urine diastase in units	Remarks
1	D. E.	June 2nd, 1935 June 14th, 1935	— —	53 42	— —	Acute colitis Improved
2	E. H.	April 30th, 1935 May 6th, 1935 June 9th, 1935	84 86 91	21 62 103	— — —	
3	M. M.	May 19th, 1935	102	89	—	
4	P. H.	Dec. 6th, 1935	74	16	—	
5	L. K.	April 16th, 1936	100	57	—	Chronic colitis
6	H. A.	June 18th, 1936	88	60	40	
7	O. B.	June 12th, 1936	100	51	—	
8	M. B.	Nov. 13th, 1936	100	100	20	
9	Ch. W.	Nov. 20th, 1936	80	63	80	
10	M. Sh.	Nov. 20th, 1936	22	52	40	
11	Sh. L.	Nov. 17th, 1936	125	53	40	
12	F. H.	Nov. 27th, 1936	91	101	80	
13	D. M.	Dec. 11th, 1936	93	80	60	
14	G. M.	Dec. 16th, 1936	102	62	40	
15	Sh. M.	Jan. 1st, 1937	111	53	80	
16	S. H.	Feb. 12th, 1937	91	61	—	
17	Sh. Sh.	Feb. 12th, 1937	100	46	—	
18	R. R.	March 5th, 1937	93	57	—	
19	E. Sh.	March 5th, 1937	93	60	—	

TABLE IX
Blood and urine diastase in patient (R.S.H.) suffering from gall stones and cholangitis

Date	Blood sugar in mg. %	Blood diastase	Urine diastase in units	Stool	Remarks
June 14th, 1935	109	160	—		
June 17th, 1935	—	—	40		
June 24th, 1935	176	44	—		
July 7th, 1935	94	53	—		
Aug. 18th, 1935	120	117	—		
Sept. 16th, 1935	137	323	50	Stercoblilin neg.	Sept. 1st, 1935, choledochotomy; removal of stones
Sept. 17th, 1935	84	542	—	Stercoblilin traces	
Sept. 18th, 1935	119	93	10,000		
Sept. 19th, 1935	—	—	10,000	Stercoblilin pos.	
Sept. 20th, 1935	—	—	10,000		
Sept. 22nd, 1935	109	191	—	Stercoblilin pos.	
Sept. 27th, 1935	—	—	625		
Sept. 27th, 1935	—	—	10		
Oct. 11th, 1935	112	124	—		Jan. 2nd, 1936, second choledochotomy; removal of stones; no complications
Feb. 10th, 1936	—	—	40		
Feb. 27th, 1936	—	—	50		
Feb. 28th, 1936	105	104	40		

quadrant and signs again indicating occlusion of the common duct. Stones were again found and removed from the common duct. The patient made an uneventful recovery.

COMMENT

The present data justify the conclusion that blood diastase, determined by the method of Somogyi, is definitely lowered in liver damage produced by hepatic and biliary disease, particularly of long duration. It seems to us of particular importance that the improvement of the general condition of the patient, as well as of the liver function, is accompanied by a rise of the diastase level of the blood. On the other hand, progressive symptoms of the liver disease and further impairment of the liver function lead to further lowering of the blood diastase. In using the diastase estimation in the blood as an aid in the evaluation of liver function in diseases of the liver and biliary tract, repeated determinations during the course of the illness give an indication of the trend and are therefore of much more value than a single determination. We have been careful to avoid the term "liver function test" since there are numerous instances of elevated or lowered levels of blood diastase in other diseases, which cannot be definitely considered an expression of a disturbance of hepatic function.

The mechanism which leads to the depression or even disappearance of diastase from the blood in liver damage is not clear—and it lies outside the scope of this investigation. Zucker and his collaborators, who like Davis and Ross (5), have observed a lowering of serum amylase in animals after liver injury by chloroform, believe that this effect is through the pancreas. On the other hand, Crandall and Cherry (6) claim that in pancreatic lesions or ligation of the pancreatic ducts, it is not the condition of this organ that influences serum enzymes, but that secondary changes

in the liver control enzyme level in the blood in virtue of an alleged enzyme destroying power of the liver.

For clinical purposes the effect of the liver in depressing the diastase level of the blood must be considered in using diastase as a diagnostic procedure in diseases of the pancreas. We believe we have demonstrated this in the above mentioned instances where liver impairment was associated with involvement of the pancreas and pancreatic dysfunction. Whereas the latter leads to a rise of blood diastase, the accompanying liver damage will depress it. In an extensive study of diastase excretion in the urine in cases of jaundice, Milbourn (7) found high values in common duct stone but rarely in parenchymatous diseases of the liver. He noticed that the duration of the jaundice appears to be of considerable significance for the occurrence of increased or normal diastasuria in cases of jaundice due to common duct stone, increased diastasuria being commoner at the beginning of the jaundice. This is an indirect proof that with progressive liver injury the diastase diminishes even in those instances where the pancreas is responsible for its rise.

The present investigation confirms the observation made by other workers in this field that blood diastase determinations are of greater value and significance than urine diastase determinations.

CONCLUSIONS

1. The Somogyi method for diastase determination in the blood gives satisfactory and fairly constant results.
2. The blood diastase is lowered in liver damage produced by various parenchymatous diseases of the liver.
3. In using diastase determination as a diagnostic it is depressed in the majority of chronic conditions.
4. In diseases of the gall bladder the blood diastase

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procedure in diseases of the pancreas the effect of the liver on blood diastase must be considered.

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Quantitative Studies on a Case of Migraine*

By

RIVKAH FAINER, M.D.

HAIFA, PALESTINE

WITHIN recent years a number of reports have appeared concerning the problem of migraine. As a chief factor partial dysfunction of the sympathetic system has been suggested. Dean Clare, Héloïse Hough and H. G. Wolff, *Arch. Neurol. Psychiatry*, 35 (1936) obtained simultaneous records of the systemic arterial blood pressure and the cerebro-spinal fluid pressure inducing experimental headache by means of histamine with its vasodilatory action. Aubry, Thiodet and Ribère, *Compt. Rend. soc. biol.*, 122 (1936) have proved that the serum albumin-globulin ratio is above

Subject, R. F., female, aged 32, weight 56, 5 kg., height 158 cms. Clinically any other cause of headache had been excluded.

The basal metabolism has been determined by use of the Knipping apparatus, patient being held under basal conditions. A high carbohydrate diet was given previous to the fast in order to secure a glycogen store, as the patient has always proved to have a blood sugar level below the normal. Castor oil was administered on the evening preceding the fast and on the third day of fasting. The subject did not change her

CHART I

Dnys of Fasting	BASAL METABOLISM				Urinary Nitrogen gms. per day	Blood Sugar mgs. %	Residual Nitrogen of the Blood mgs. %	Body Weight in kgs.	Remarks
	Respiratory CO ₂ mgs. per minute	O ₂ consumed mgs. per minute	Respiratory quotient RQ	Deviation from normal %					
0	348	326	.78	+ 18% (Harris-Benedict Standard)	6.1863	69.4	19	56.5	Those determinations were made at the beginning of fasting, patient being previously on a low protein and a high carbohydrate diet, after a long period of headache.
1	293	269	.79	—	7.00	67.2	68.6	56.3	No headache.
2	287	272	.77	—	5.824	85.2	88.7	55.1	No headache.
3	286	266	.78	—	6.496	—	67.2	54.7	No headache.
4	273	204.6	.67	—	*	33	40	51	At the onset of a severe attack of migraine after ½ hour vomiting began, which lasted about 10 hours.

*On this day the urine has been collected partly 1 c.c. contained 16.24 mg. N.

normal and the departure from the normal is greater during the period of calm between attacks than during attacks themselves.

Our knowledge of the etiology of migraine is still obscure and it would lead us too far to discuss this matter.

The present research has been undertaken to study the metabolic changes in a case exhibiting all the classical features of typical migraine.

Experimental:

To minimize the influence of food and putrefaction products we studied the basal metabolism during the fast.

ordinary activity during the time of starvation. She took daily 3 cups of tea with sugar, about 12 gms. in all.

The determination of the carbon-dioxide combining power was also carried out under basal conditions. Blood was drawn without pressure from the vena cubitalis and centrifuged under paraffin oil in presence of sodium oxalate and fluoride. Plasma was used for the analysis. The CO₂ was estimated by means of a Van-Slyke closed manometric apparatus, the Van-Slyke-Sendroy tables being used for total CO₂ and expressed in volumes per cent.

The pH was measured by colorimetric method. Blood sugar was determined by the micro-method of Hage-

*From the Scientific Research Laboratory, Haifa.

CHART II

Day of Starvation	Non-Protein Respiratory Quotient	Carbohydrate Calories per Day	Carbohydrate gms. per Day	Fat Calories per Day	Fat gms. per Day	Protein Calories per Day	Protein gms. per Day	Total Calories per Day	Remarks
0	0.77	300.96	80.5	1107.48	119.1	163.92	38.66	1572.36	
1	0.79	311.76	83.00	789.60	84.9	185.52	45.75	1286.89	
2	0.76	206.05	55.00	932.38	100.2	154.38	36.43	1292.81	
3	0.77	237.88	64.1	869.52	93.5	171.36	40.6	1278.76	
4	0.65	0	0	935.60	100.6	171.36	40.6	1106.96	During attack of Migraine.

CHART III

CO ₂ mgs./minute	O ₂ mgs./minute	RQ	Remarks
348	326	0.78	After 14 hours of fasting and rest for 2 hours.
393	300	0.87	½ hour after intake of 1 grain of amidopyrin.
400	300	0.96	1½ hours after a mixed meal which consisted of: 80 gms. bread, 50 gms. white cheese, 2 eggs, 30 gms. butter, 1 orange, 1 cup of tea and 4 gms. sugar.
429	310	1.01	2½ hours after the meal.

dorn-Jensen. For analysis of residual nitrogen the modified Bang micro-Kjeldahl method was applied. The serum calcium was examined by precipitation with ammonia-oxalate, centrifuging and titrating with a 0.01 normal solution of potassium permanganate.

The results of those analyses are given in Charts I, II and IV.

The respiratory CO₂ diminished gradually from day to day, whereas the amount of oxygen consumed showed some fluctuations, though there was generally a tendency towards decrease, the respiratory quotient remaining nearly constant until the fourth day.

The marked rise of the blood residual nitrogen may have been due to the cleavage of protein bodies. It is a well known fact that its amount is higher in starvation than in normal conditions. There is nearly no

change in the blood sugar level after one day fasting, its yield being increased about 23 per cent on the second day.

A close correlation between the amount of blood sugar and non-protein nitrogen was evident, the amount of both being nearly equal during the time of starvation.

It should be noted that the patient felt quite well during the first three days of the fast, as she was absolutely free of headache. On the fourth day an attack of migraine occurred, accompanied by nausea and vomiting. This attack was associated with a pronounced fall of the respiratory quotient and a striking drop of both blood sugar and residual nitrogen. A glance at Chart II will make it evident that no energy was at that time supplied by carbohydrates, as the store of blood sugar was nearly exhausted.

Further examinations made on the patient proved that severe attacks were always associated with a marked drop of blood sugar, even when blood was taken about two or three hours after meal.

We also studied the influence of drugs and a mixed diet on the metabolism of the above patient. The results are given in Chart III.

Other data are given in Chart IV. The amount of serum calcium is decreased between attacks, whereas there is a striking rise in the calcium level after a severe attack with vomiting.

The CO₂ combining power somewhat exceeded the normal limits. It was of interest to us to compare the

CHART IV

Remarks	Serum Ca mgs. per cent	Uric acid (oxalate blood) mgs. per cent	CO ₂ combining power of the plasma. Volumes per cent	PH Plasma unsaturated with CO ₂	PH Plasma saturated with CO ₂	Allantoin in the urinary sediment	Urinary N daily amount gms.	Urinary amino N daily amount gms.	Ratio whole — N NH ₂ — N %
Migraine Patient R. F. Blood drawn when free of migraine.	7.32	1.32	67.2		—		9.475	0.268	2.4
Migraine Patient L. G.	7.30		68.37	7.4	—				
Epileptic Patient.	7.00		—	—	—				
Patient R. F. Blood drawn at the end of a severe attack.	12.00		—	—	—	+++			
A healthy subject. Vegetarian.			53	7.4	7.0				

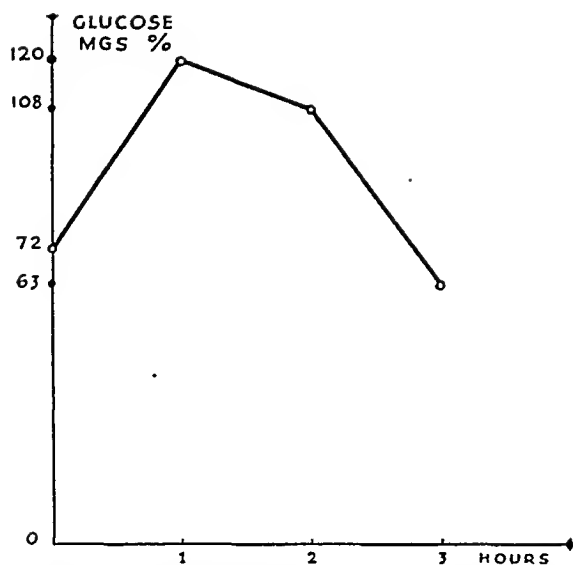


Chart IV. Sugar tolerance test. 90 gms. of sugar with lemon juice were given. Average of 3 tests.

results obtained with another normal ease where an increased CO_2 power could have been expected. Blood of a healthy subject, vegetarian for more than twenty years has been therefore examined and the total CO_2 found still higher. The quantity of uric acid was re-

duced. Allantoin, identified as such by microscopic examination as well as by chemical test, has always been present in the urine in considerable amounts after severe attacks.

Our interest was aroused by the fact that the amount of reducing sugars of the blood has always proved to be below the normal value (65-78 mgs. per cent), even when the subject was previously kept for some time on a high carbohydrate diet. An increased sugar tolerance was therefore suggested. A test made has confirmed this suggestion. The results of the test are given in Chart IV.

SUMMARY

In the case of migraine studied, a decrease of reducing blood sugar, residual nitrogen, uric acid and calcium was found at times between attacks. The sugar tolerance is increased and the CO_2 combining power of the plasma was on the upper limits. During attacks a marked drop of the blood sugar was noted. Allantoin appeared in the urine after severe attacks, the blood serum calcium being about 28.5 per cent higher than at calm between attacks. The amount of blood sugar was not reduced during starvation, its value being higher than normal on the second day of fasting.

Further investigations are in process.

I wish to express my gratitude to Mr. Mose Wilbushovich, founder of the Scientific Research Laboratory, Haifa, who has enabled me to make this study, and to Miss Lea Olshansky for making the gaseous metabolism determinations.

Editorials

THE DIET OF PRIMITIVE AND ANCIENT MAN

PRIMITIVE man must have been a hunter. He chased and killed before he feasted. He collected seeds of wild grass, soaked them in water or mashed them between stones. Wild grasses grew in spots, primitive man ate only the seeds of these cereals, therefore he was fortunate to be in the right place at the right time and season to enjoy a wild wheat, barley, millet or rice meal. The food-accessory substances or vitamins in such seeds were of great health value to these folk. Growth, reproduction and maintenance were aided by ingesting the seeds of these cereals. Primitive man was primarily a meat eater. The pelts of animals he killed for food served as insulations during the cold weather. These were an ever moving folk, seeking shelter only when it was necessary for survival. Ventilation was of no concern to primitive man. The physical exertion coincident with the acquisition of food, insured a good appetite. He was not troubled with overweight.

Man very early acquired the ability to control some of the forces or factors in his environment. This reacted to his advantage. So long as he was a collector of wild seeds and a hunter of wild animals, he experienced considerable competition. The herbivorous animals fed upon wild grasses before, during and after the seeds ripened. Carnivorous animals were not only his competitors but his enemies. When man began to tame some wild herbivorous animals, he insured

himself a good food supply. When man began to plant the seeds of the wild grasses, he also reaped a harvest of food. He used the tame animal to increase his acreage of planting, to bear his heavy loads. He now had property. This was the beginning of an organized social system. He and his neighbor had something in common and they agreed to unite and protect their property.

Omitting a gradual development of man and his diet from early to modern times, we can think for a moment about how different our present environment is to that mentioned in the preceding paragraphs. During the last fifty or sixty years man has made rapid progress in controlling his environment. He has by physical, chemical and biological measures so changed the world in which he lives that only the outdoor air and weather conditions remain beyond his control. He can synthesize, concentrate, refine, refrigerate, and preserve his food. Rapid transportation allows him to have tropical, semi-tropical or arctic food during the whole year. His diet is no longer regulated by seasonal climatic conditions. He can live in houses constructed like incubators, temperature of the inside air can be regulated to suit his own sense of comfort. Ventilation becomes an important problem. These artificial changes in our environment have not been made during the span of one life time. It required many, many thousands of years for man to adapt himself to changes in environment during the

natural process of evolution. Some of these changes extending over centuries were much less drastic than the way we have artificially changed our environment during the last three decades.

From the primitive stone-throwing hunter and collector of seeds of wild cereals to the pastoral and to the agricultural forms of civilization was indeed a slow process. The acquisition of food was the big stimulus behind this movement. Diet has played a tremendous role in history of man. When he was able to accumulate enough food to satisfy his body needs and even store an excess in ease of necessity; then he had time to wonder why day followed night and why the moon changed in shape after a cyclic manner. With a leisure or land owning class of people emerging from such a civilization, we find records of some of the things they thought about. The great architectural monuments and the writings we now possess of Egypt, of ancient Greece, of Italy, of Assyria, of northern Africa and of north China were all produced by cultivators and consumers of wheat. The monuments and letters of southern India, of the Hindu-Chinese countries, of south China, of Java and of Sumatra were the products of rice-cultivating and a rice-consuming folk. The massive and extensive monuments of ancient Mexico and Peru have been left by corn cultivators and corn consumers. The hunting and pastoral people lead a wandering and nomadic life. The struggle for existence tended to develop a fierce and fighting type of man. The hunting folk attacked the herds of the pastoral people, the latter multiplied faster because of their better and more dependable food supply. The pastoral folk all through history and even at the present time lead a nomadic life and attack the agricultural people at each and every opportunity.

We find the ancient folk used the milk of their domesticated animals for food. It is interesting to note that they soured the milk before ingestion. Throughout the east soured milk is called "leben." The Egyptians boiled the milk of their buffalo, cow or goat, allowed it to cool to open air sun temperature and added some previously soured milk from the day before. The fermentation was rapid and was completed in about six hours. The technical procedure varied with the various people, but soured milk was extensively used in Egypt, Palestine, India, Arabia, Turkey, Balkan States, etc.

Grapes were cultivated by these ancient people to make wine and vinegar. Wine is an acidulated alcoholic beverage. Vinegar was widely used as a preservative for various kinds of fruits and other perishable foods. When viewed as a whole, that is when their total available food is taken into consideration, one cannot but be impressed with the acidified diet ingested by these ancient people living together in communities in the cradles of civilization.

We know that the Roman legions added some vinegar to their cup of water while marching and fighting in foreign countries. This was evidently the result of experience. We are told that this kept these soldiers from having pestilence and diseases common to the various countries they were invading and policing. A cup of water with a little vinegar added is a refreshing drink to a tired person. The Biblical reference to the placing of vinegar upon a sponge to Christ's lips during his crucifixion was a humane act on the part of the Roman soldiers. This is what they

were accustomed to doing to exhausted and wounded comrades. We are informed in the Book of Ruth that the reapers in the harvest fields refreshed themselves by dipping their bread in vinegar before eating it.

Some idea of an ancient feeding habit of man can be gained from the camel drivers on the deserts. These people allow the camel's milk to sour, then evaporate it to a solid consistency. This forms part of a camel drivers food while on the desert. He sits in the shadow east by his camel, adds water to a handful of this "soured milk powder" to suit his taste and thirst. The small shady spot in which he sits is cool in contrast to his previous hours in the hot sunshine. He slowly drinks his lunch in comfort.

Sir Austen Layard in recording his experiences in the desert some seventy-five years ago, states that the Bedouin's food consists of wheaten bread, a few wild herbs, such as asparagus, onions, garlic, some fresh butter, curds and sour milk. The milk of their sheep and goats was shaken into curds and was rarely or never drunk fresh. This author mentions that fresh milk was unwholesome when drunk in the hot desert climate and states that he can vouch for this from personal experience. The sour milk or leben was their principal food. He further states that the Bedouins enjoyed a freedom from sickness and possessed an extraordinary power in withstanding fatigue. Cholera and other diseases never were epidemic among these people. Smallpox was their greatest pestilence.

The acid-base equilibrium of the contents of the stomach and upper part of the small intestine is an important factor in maintaining health. Diet plays a role in the reaction of the contents of this part of the alimentary tract. The ingestion of acid-buffered food assists in the maintenance of an excess of acid over alkaline reacting substances in the stomach and upper half of the small intestine. This is particularly true if there is a deficiency in the acid secreting power of the stomach. The advantages of acid-buffered foods in infant feeding illustrates this principle.

The biological nature of the controlling mechanism of the bacterial flora of the intra-intestinal contents was summarized in a previous editorial (Amer. Jour. Dig. Dis. and Nutrit., 4:603, 1937). The feeding habits of ancient man were sound and scientific in view of our present state of knowledge.

Lloyd Arnold, Chicago, Ill.

A SUGGESTION AS TO THE MODE OF PUBLICATION OF THERAPEUTIC RESULTS

ONE of the everyday problems of editors of medical journals is what to do with papers reporting brilliant results in the treatment of disease with some new drug. Every student of therapeutics knows that every time a new drug catches the fancy of physicians or proves to be useful in one small field of disease, it is immediately tried out extensively for the relief of almost every known malady. Always, at the beginning, many laudatory articles are written, and then, after months or years, it becomes apparent that either the remedy had no value at all, or else it was useful in the treatment of only one or more closely related conditions.

Thus, a century ago, quinine, having been found wonderfully helpful in malarial fevers, was promptly

used in the treatment of all other fevers. From this success the idea grew that it must be a great tonic; hence, it soon was being used in the treatment of depressed states and anemias of all kinds. Today, the pharmacologist would probably say that its usefulness outside of the field of malaria is doubtful, and the better trained and the more thoughtful a physician is, the more likely he is to use the drug only for the treatment of malaria.

Similarly, some forty years ago creosote was thought to be an excellent remedy for tuberculosis; because of its reported success in this field, the drug was widely used for colds and coughs of all kinds, and later it was given as a tonic. Today, I doubt if one could find one expert in the treatment of tuberculosis who would think of giving it to his patients. With its horrible and long-lasting taste, it is a miserable drug to give, especially to children, and so far as anyone can really tell, it is of no value in any known disease.

All physicians can remember how, twenty years or so ago, benzyl benzoate flashed on the horizon, and soon was curing almost everything, including hypertension and leukemia. Today, about its only value seems to be in relieving some patients with painful menstruation.

One of the most curious features of the development of therapeutic practice is the way in which the medical profession will give up a drug, which, according to most reports, is still curing in 90 per cent or so of cases, to try a new one. One would think that men who had once found a marvelously efficient drug would never give it up. But to judge from articles in the journals in the last few years, the profession shifted its favor rapidly from gastric mucin to vegetable mucin, then to a mixture of foreign protein and emetine, and then to commercial brands of histidine, all at a time when, to judge by the literature, each one of these substances was giving almost perfect results in the treatment of ulcer.

Today, sulfanilamide is being tried out in the treatment of all infections, just as salvarsan was tried out twenty years ago. Today, salvarsan is used in the treatment of syphilis, yaws, — some intestinal parasites, and little else. Similarly, in a few years the use of sulfanilamide will doubtless be restricted to a few types of infection.

Obviously, no one can object to the widespread trial of useful or supposedly useful drugs. The only objectionable feature of the process is the cluttering up of the literature with the first highly favorable reports of men whose enthusiasm must have outrun their judgment. Certainly when the excitement died down no one could duplicate their results. As some cynic once said to a sick physician, "For goodness sake, take a few doses of this new drug while it is still curing!"

Actually, what is one to think about the small mountain of enthusiastically favorable articles which is always piled up after the discovery of some new drug which takes the fancy of the profession. When, with the passage of time, it becomes obvious that the

writers were wrong—when tuberculosis no longer responds to the curative action of creosote, and high blood pressure no longer returns to normal under the influence of benzyl benzoate—what is one to think about the writers of the favorable articles? Surely they did not all consciously belong to the Ananias Club of Roosevelt the First. No, probably what happened in most cases was that these men never thought to carry out their therapeutic experiment in such a way and with so perfect a control group that a trained statistician could tell what value to place on the results. What with the natural tendency for many diseases to grow better, the commonly overpowering tendency of optimistic persons, physicians and patients alike, to fool themselves, and the lack of such wide experience as would tell a physician whether or not the results obtained with a new treatment are better than those obtained with old methods or none at all, it is little wonder that most of the reports as to the efficacy of new drugs are of no value. Worse yet, a new drug for the treatment of, let us say, ulcer, is usually given *in addition* to the usual dietary and alkalinizing treatment of ulcer.

Often then, as an editor looks at the pile of therapeutic reports that come to his desk, his tendency is to send them back; he hates to think of padding the files of his journal with a mass of articles which are almost certain to be worse than useless later. But then he will wonder, "Perhaps there is a grain of truth here, and I should not be denying it publication." But, as he rereads the long article with all its ease reports, he asks, "Is all this necessary? Why couldn't the man have said simply that he tried so-and-so's new medicine in thirty cases of ulcer, and his impression was that the patients did better than they would have done on diet and Sippy powders alone?" What reams of paper this would save, and actually how often the writer's object would be better served with the short, pithy, readable report than with the long tiresome one.

Other physicians, noting such a report, might be induced to make similar studies; they also might make short reports, favorable or unfavorable, and soon the rank and file of the medical profession would gain a good idea of what drugs are worth trying and what are not. Unfortunately, today, few men write unfavorable reports, perhaps because they assume that every paper must be a long and detailed one, and they haven't time to spend over a "dead horse." Actually, how helpful and simple it would be if soon after a new and popular drug was introduced, notes like this would appear: "I tried the drug in such and such dosage in twenty cases of this and that with apparently good beginning results in some. In two cases the results seem to be fairly permanent. In several cases I had to stop administration because of abdominal pain, diarrhea, and skin eruptions, and in one case the patient promptly died with a severe leukopenia. I have decided to stop using it. Signed"

Walter C. Alvarez, Rochester, Minn.

Book Reviews

The Principles and Practice of Rectal Surgery. By Wm. B. Gabriel, M.S., F.R.C.S., Surgeon to St. Mark's Hospital and Royal Northern Hospital, London. Second edition, 353 pages, illustrated. H. K. Lewis & Co., London, 1937.

THIS second edition of "The Principles and Practice of Rectal Surgery," by Mr. Gabriel, is presented five years after the publication of his first edition. This volume is a detailed record of the experience and progress in the diagnosis of rectal ailments and the practice of this branch of surgery, which the author has collected during his affiliation as surgeon to St. Mark's Hospital for Diseases of the Rectum since 1920.

It has been a pleasure for the reviewer to read a book so clearly written and well illustrated. The whole field of rectal surgery is covered in a most thorough and painstaking manner. Its contents are a record of the personal experiences of the author both from his hospital and his private practice. One reads a story of the progress and refinement in treatment of diseases of the terminal bowel.

The second edition is noted particularly for its newer work on surgical anatomy contributed in collaboration with Mr. O. V. Lloyd-Davies, M.S., F.R.C.S. and represents much of the recent work of Milligan and Morgan. Local anaesthesia has found its rightful place in non-suppurative lesions. The injection treatment for haemorrhoids has been found to be applicable in only about 40% of the cases. The operation of rectosigmoidectomy for intractable prolapse of the rectum is carefully described. Mr. Gabriel has made the timely observation that a certain percentage of fistulae-in-ano eventually become malignant. In the new material one also notes: the role of epidermophytosis in pruritus ani—injuries of the rectum—lymphogranuloma inguinale and many new refinements of technique and post-operative care.

The chapters on benign and malignant tumors of the terminal bowel are thorough and extremely well written. Mr. Gabriel's perineo-abdominal operation for cancer of the rectum presents itself as one of the most important features of the volume. The role that benign adenomata play in rectal cancer has been emphasized. This book can be highly recommended to those who seek a special knowledge of diseases and injuries of the terminal bowel.

E. A. Daniels, Montreal, Canada.

Practical Methods in Biochemistry. By Frederick C. Koch, Ph.D., Professor of Biochemistry, University of Chicago. Price, \$2.25. 302 pages, 17 figures, Second Edition. William Wood & Company, Baltimore, 1937.

THIS excellent laboratory manual of Biochemistry for medical students has been carefully revised and brought up-to-date. The book is excellent in regard to the choice of experimental methods, the clarity with which the methods are described, and the choice and presentation of tabular material.

The general laboratory instructions, included as an

appendix, are exceptionally worth while and every student technician, laboratory worker, or physician, who occasionally does work in the chemical laboratory, would do well to read this part of the book even if he or she did not read the remainder. The first sentence of this appendix reads: "Orderliness, intelligent manipulation, neatness and precision are absolutely necessary for success in any laboratory work."

A. C. Ivy, Chicago, Ill.

Traitement des Constipations Fonctionnelles Treatment of the Functional Types of Constipation. By Gabriel Leven et Roland Leven Masson et Cie Paris, 1938.

A BOOKLET of some 87 pages in which the authors make pertinent remarks, on what may be regarded by a few as a commonplace subject but nevertheless presents in a concise manner the authors' viewpoints on constipation and auto-intoxication, based on clinical observations and laboratory findings.

One is to bear in mind of what vital importance is the defensive barrier played by the intact intestinal mucosa in constipation and the therapeutics thereof is to maintain a sound intestinal mucosa.

Furthermore, the frequency of the spastic type of constipation even in elderly patients indicates that the treatment must take into account the relief of the spasm.

Whilst we are fully aware how a treatment based on drastic purgatives the misuse of enemas and the abuse of a roughage diet, in the presence of such findings is foolhardy; we fail to grasp why such a treatment must be considered as the classical technic in contrast to the treatment advised by the authors which as they maintain, respects the intestinal mucosa and relieves the spasm.

There is some interest in recognizing three distinct functional types of constipation: (a) constipation appearing as a spurious symptom met with so often in infants as well as adults, being the outcome of defective hygiene, malnutrition or obesity; (b) physiological constipation, which makes its appearance following an operation, or pyrexia, and most frequently met with in vicarious vomiting of pregnancy. This constipation should not be tampered with; being a physiological phenomenon of defense; we should mark time and wait for the spontaneous return of stools in all these cases. There are numerous cases to illustrate this point. We doubt, nevertheless, if most surgeons will subscribe to this mode of thinking: (c) pathological constipation, medical or surgical. Under this heading the authors consider only that type of constipation which is the outcome of a medical condition such as hyperchlorhydria, in which, increased acidity brings about spasm of the intestinal tract; biliary tract infection, aerophagia and dystrophy of the abdominal muscles.

More debatable is the author's viewpoint, that some intestinal anomalies such as dolichocolon may be responsive to medical treatment.

Following this exposé the second part of the work is given to a brief outline of the therapeutic methods employed in relieving the spasm present in the intestinal tract and in protecting the intestinal mucosa against further damages.

The full armamentarium, from the avoidance of roughage food to glandular therapy; the treatment of anal fissures, and hemorrhoids; gymnastics and massage, must be taken into account whilst dealing with this topic on therapeutics. The authors speak highly of the good results obtained by sodium bromide in spastic constipation and the most encouraging effects of sodium cacodylate used as a suppository in anal fissures.

In addendum, the authors have demonstrated by sketches their method in applying the abdominal band in constipation with enteroptosis, a most ingenious and interesting procedure.

A. Cantero, Montreal, Canada.

Cirurgia de Megaesôfago. By Edmundo Vasconcelos and Gabriel Botelho. Sao Paulo, Companhia Editora Nacional, 434 pp., 1937.

VASCONCELOS and Botelho, working with a number of associates, have prepared an interesting volume of 434 pages on the problem of megaesophagus. This disease appears to be much more common in Brazil than in North America. The writers incline to the view that the trouble is due commonly to destruction of ganglions and nerves, not only in the wall of the esophagus but also outside in the vagal trunks. They believe also that these nerve changes are associated with a lack of vitamin B₁ in the diet, and a tendency to the development of beriberi. The writers describe in detail the various operations and procedures that can be used to overcome the cardiospasm. They describe also the innervation of the normal esophagus.

Unfortunately, the book is written in Portuguese, a language which is not well understood in this country, but it can be read fairly well by anyone who understands Spanish.

The Therapeutic Problem in Bowel Obstructions. By Owen H. Wangenstein. Published by Charles C. Thomas, Springfield, Ill., 1937.

IN a review of a large amount of experimental work on the factor of distension the author traces the pathogenesis of intestinal obstruction through its various stages and concludes that no direct and unequivocal statement of the lethal factors in intestinal obstruction has been made. The loss of fluids, leading to loss of electrolytes, elevation of non-protein blood

introgen and the shift to acidosis, occurs concomitantly with the changes in circulation, bacterial relations, and absorption from the bowel.

The recognition of obstruction is fully discussed as is the differentiation of large and small bowel obstructions. The check-valve action of the ileo-cecal valve is pointed out. X-ray films are valuable aids in locating the probable point of obstruction.

In the treatment of obstructions, saline solutions, blood transfusions, conservative decompression, and operations are indicated. Saline solutions and blood transfusions are indicated as pre-operative measures. In those cases in which incomplete obstruction is due to adhesive processes, and in which no strangulating mechanism obtains decompression by suction applied to a duodenal tube is best adapted. Likewise, partial obstructions associated with inflammatory lesions are frequent indications for this type of treatment.

Conservative suction decompression is contra indicated in any case in which strangulation of the bowel has occurred and those cases of acute obstruction of the left half of the colon, in which the colon has been converted into a closed loop by the ileo-cecal valve.

The "ear-marks" of successful decompression are (1) cessation of gas pains, (2) decrease of distension, (3) visualization of gas in the colon, (4) less fluid aspirated through the duodenal tube, and (5) toleration of temporary discontinuance of the suction without recurrence of pain. No narcotics should be given to the patients receiving this treatment. In support of the view that there is probably no toxic absorption factor in small bowel obstructions the author points out that no evidence of such absorption is seen as long as the bowel wall remains viable.

The most important single factor in the operative treatment of these cases is the rigid observance of strict asepsis. When a closed loop of colon is found it may be wise to establish an ileostomy passing the tube down through the ileo-cecal valve rather than attempt any manipulation of the cecum itself.

Part II deals with the diagnosis of acute abdominal disorders and describes the indiscriminate employment of laparotomy as a diagnostic procedure. The possible methods of treatment are discussed in detail and the management of the suction apparatus shown. Excision of non-viable bowel with the establishment of a double barrel enterostomy is recommended rather than immediate anastomosis. Post-operative treatment is discussed in detail.

In Part III all of the unusual and rare causes of obstruction and their distinctive features are discussed.

Large bibliographies and numerous figures accompany each part of the book.

N. M. Percy, Chicago, Ill.

Program of the Forty-First Annual Meeting of the American Gastro-Enterological Association

ATLANTIC CITY
Monday and Tuesday, May 2 and 3,
1938

Headquarters and All Sessions
HOTEL CLARIDGE

MONDAY, MAY 2, 1938

Morning Session, 9:15 A. M.
Daylight Saving Time

Memorial Address: Elmer Eggleston
by Burton R. Corbus.

Presidential Address: Ralph C.
Brown, Chicago.

Carbonate Excretion in the Urine as an
Indication of Alkalosis: Lee C. Gate-
wood, Chicago.

Variations in the Enzymatic Activity
of Duodenal Contents: Victor C.
Myers and (by invitation) Alfred H.
Free, Argyl J. Beams, Cleveland.

History and Development of Gastric
Analysis Procedure: Franklin Hol-

lander and (by invitation) Abraham
Penner, New York.

The Triple Mechanism of the Chemical
Phase of Gastric Secretion: Boris P.
Babkin, Montreal, Canada.

The Present Status of Treatment in
Chronic Gastritis. Gastroscopic Ob-
servations: William A. Swalm and
(by invitation) Lester M. Morrison,
Philadelphia.

Psychiatric Contributions to the Study
of the Gastro-Intestinal System:
Earl D. Bond, Vice Dean for Psy-
chiatry, University of Pennsylvania
Graduate School of Medicine, Phila-
delphia (by invitation).

Adjournment for Luncheon, 2:15 p. m.

Studies on the Use of Aluminum Hydro-
xide Gel in the Treatment of Peptic
Ulcer. Edward S. Emery, Jr., and
(by invitation) Robert B. Ruther-
ford, Boston.

The Vitamin C Cevitamic Acid Re-
quirement of Patients on Ulcer Man-
agement: Donald T. Chamberlin and
Harold J. Perkin, M.A., Boston (by
invitation).

Vagotomy in the Surgical Therapy of
Peptic Ulcer: Asher Winkelstein and
Albert A. Berg, New York.

Healing and Recurrence of Gastric
Ulcer—A Clinical, Roentgenological
and Gastroscopic Study: Walter L.
Palmer, Frederick E. Templeton (by
invitation) and Rudolf Schindler,
Chicago.

Early Cancer of the Stomach and Its
Clinical Significance: William C.
MacCarty, Rochester, Minn.

Executive Session—Associate Mem-
bers are requested not to attend.

Annual Dinner, 7:30 p. m., Hotel
Claridge, Atlantic City, N. J.

Dr. William R. Houston, Professor
of Medicine, University of Texas,
Austin, Texas: "Our Relations With
the Orient."

Christopher Morley, Essayist, Novel-
ist, Columnist: "Change Without
Notice."

TUESDAY, MAY 3, 1938

Morning Session, 9:15 A. M.

The Diagnosis of Colitis Associated
With Virus of Lymphogranuloma
Venereum by Bowel Antigen: Moses
Paulson, Baltimore.

Late Results of an Epidemic of Bacil-
lary Dysentery: Philip W. Brown,
Rochester, Minn.

Polypoid Adenoma and Adenocarcinoma
of the Colon: Paul Klemperer, New
York.

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Study of the Normal Gall Bladder:
Heinrich Necheles, Chicago.

The Problem of Gall Bladder Infection:
Martin E. Rehfuess and (by invitation)
Guy M. Nelson, Philadelphia.

The Etiological Relationship of Lesions
of the Cystic Duct to Cholecystic Disease:
Warren H. Cole, Chicago.

Adjournment for Luncheon, 2:15 p. m.

The Endocrines in Relation to the
Gastro-Intestinal Tract: James B.
Collip, Professor of Biochemistry,
McGill University, Montreal, Canada
(by invitation)

Treatment of the Tendency to Hemorrhage
in Jaundiced Patients, With
Special Reference to Vitamin K.:
Albert M. Snell and (by invitation)
Hugh R. Butt and A. E. Osterberg,
Rochester, Minn.

The Value of a Combined Study of
the Newer Laboratory Tests in the
Differential Diagnosis of Toxic and
Obstructive Jaundice Including Blood
Phosphatase, Cholesterol Partition,
Galactose Tolerance and Glucose
Tolerance: Harry Shay and (by
invitation) David Meranze, Theodore
Meranze and Philip Fieman, Philadelphia.

A Proved Case of Recovery From
Fatty Metamorphosis of the Liver
After Treatment With Lipocain:
David H. Rosenberg, Chicago.

The Response of the Canine Liver to a
Mixed Meal and to Certain Drugs
With and Without the Return of Bile
to the Intestine: Arthur J. Atkinson
and (by invitation) C. R. Schmidt
and (by invitation) J. M. Beazell,
Chicago, and Andrew C. Ivy.

The following Papers will be Read by
Title:

A Modern Conception of Gastric Secretory
Functions. Based Upon Recent
Investigations and Newer Interpretations:
Samuel Morrison, Baltimore.

The Clinical Significance of Prerenal
Azotemia in Abdominal Diseases:
Henry A. Rafsky and (by invitation)
Michael Weingarten, New York.

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THE ASSOCIATION FOR THE DEVELOPMENT OF MEDICAL RELATIONS BETWEEN FRANCE AND FRIENDLY NATIONS

The President of the A.D.R.M., Professor Henri Hartmann, Paris, has organized for June and July, 1938, post-graduate courses in English, which will be presented at the Faculty of Medicine, as well as in the hospitals of Paris, under the direction of the professors, physicians, surgeons and specialists of the hospitals.

June 27 to July 2: *Hospitol de la Pitié*: a week in **CARDIOLOGY**, under the direction of Professor Clerc, from 10 to 12 a. m., case presentations, radio-scopic, electrocardiography, etc.

June 27 to July 2: *Hôtel-Dieu*: a week in **OPHTHALMOLOGY**, under the direction of Professor Terrien: ophthalmological technique, clinical and laboratory examinations, each morning from 10 till noon.

June 27 to July 2: *Hospital Broca*:

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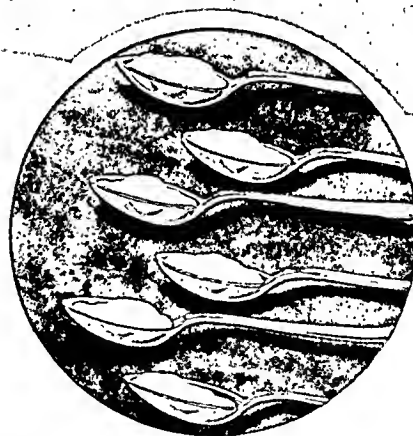
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a week in GYNECOLOGY, under the direction of Professor Mocquot, clinical examinations, operations, insufflation of the tubes, etc., each morning from 10 till noon.

June 27 to July 2: A week devoted to ENDOCRINOLOGY, by Professor Charles Richet, in the afternoons.

July 4 to 9: A week in PEDIATRICS in the various children's hospitals, by Professors Lereboullet and Debre and Dr. Armand-Delille. Clinical examinations in the mornings and ward rounds and infant feeding in the afternoons.

July 4 to 9: One week in NEURO-

PSYCHIATRY in the various hospitals with the collaboration of Professors Guillaïn, Clovis Vincent, Alajouanine, Hagueneau and Dr. Worms.

July 4 to 9: Hôpital Saint-Louis: A week in DERMATOLOGY, both mornings and afternoons, directed by Professor Gougerot.

July 4 to 9: Cancer Institute at Villejuif: Each morning from 9 till 11, Professor Verne will demonstrate normal histological technique and tissue culture.

July 4 to 9: Faculty of Medicine: Physiological Laboratory: Professor Binet and Dr. Bargeton: Medico-

surgical Physiology: Theory from 2 to 3 p. m.; practical demonstrations from 3 to 5 p. m.

July 4 and 5: Hôpital Cochin, mornings and afternoons Professor Chevassu will demonstrate urological diagnosis including pyelography.

July 6 to 12: Hospice de la Salpêtrière, each morning from 10 to 12, Professor Gosset will direct instruction on Abdominal Surgery (stomach, intestines and biliary apparatus). In the afternoons Dr. Thalheimer will review operations using the cadaver as subject.

The fee for the courses of study is 300 francs for 6 mornings or 6 afternoons and 500 francs for mornings and afternoons. For registration and reservations address the Bureau d'I. A.D.R. M., Salle Beclard, Faculté de Médecine, Paris, VIe, France.

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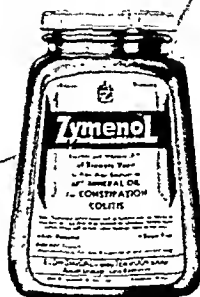
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PROGRAM

1938 Annual Meeting

SAN FRANCISCO

June 11th, 12th and 13th

SATURDAY

9 A. M.—Registration—Italian Room
—St. Francis Hotel.

10 A. M.—Opening Session—Italian Room.

Address of Welcome: Doctor Jacob Geiger, Director of Health, City of San Francisco.

Announcements: Doctor Dudley Smith, San Francisco, Chairman of Arrangements Committee.

Presidential Address: Doctor Harry Z. Hibshman, Philadelphia.

Memorials to Dr. Daniel Fiske Jones, Boston, Dr. Daniel Morton, St. Joseph, Dr. Curtice Rosser, Dallas (Secretary).

CASE REPORTS

Pathology:

Lymphopathia Venerea with Abdominal Involvement: Doctor Collier F. Martin, Philadelphia.

Lymphangioma of the Colon: Doctor Warren R. Rainey, St. Louis.

Ovarian Dermoid with Rectal Implantation: Doctor Raymond L. Murdoch, Oklahoma City.

Lymphosarcoma of the Anus: Doctor Simon B. Kleiner, New Haven.

Dermoid Cyst of Rectum: Doctor Joseph F. Saphir, New York City.

Myoma of Rectal Wall: Doctor George H. Thiele, Kansas City.

Foreign Bodies:

Intraperitoneal Foreign Body: Doctor Curtis C. Meehling, Pittsburgh.

For the Aristocracy of Thought

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enterological thought. It sees most of the manuscripts in this specialty: it prints all of them that are suitable . . . BETTER articles will be printed only when BETTER articles are written. The reader may confidently believe that at present the best work in gastro-enterology finds its way into these pages . . . Another way of saying that the management of this JOURNAL is seeking to perfect a really worth-while Archive in a most important field.

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The Contents Of The June Journal Will Be As Follows:

THE PROCESS OF INTESTINAL ROTATION IN THE HUMAN BEING ILLUSTRATED BY THE DRIED INTESTINES OF THE CAT	E. G. Wakefield, M.D., C. Stuart Welch, M.D. and Charles W. Mayo, M.D.
GASTROSCOPIC STUDIES	Fred A. J. Geier, M.D.
RESULTS OF RADIATION THERAPY IN PRIMARY OPERABLE RECTAL AND ANAL CANCER	George E. Binkley, M.D.
A SIMPLE TEST FOR DETERMINING THE PRESENCE OF GASTRO-INTESTINAL LESIONS. PRELIMINARY REPORT	Edward E. Woldman, M.D.
THE EFFECTS OF ACETYLCHOLINE, ACETYLBETAMETHYLCHOLINE AND PROSTIGMINE ON THE SECRETION OF THE STOMACH OF MAN AND DOG	H. Necheles, M.D., Ph.D., W. G. Motel, M.D., J. Kosse, M.D. and F. Newell, M.D.
THE TAKATA REACTION IN THE BLOOD SERUM	Edgar Wayburn, M.D. and Clifford B. Cherry, M.D.
CHRONIC ULCERATIVE COLITIS: AN ANALYSIS OF 88 CASES	Isidore A. Feder, M.D.
THE VITAMIN B COMPLEX AND FUNCTIONAL CHRONIC GASTRO-INTESTINAL MALFUNCTION: A STUDY OF TWO HUNDRED AND TWENTY-SEVEN CASES	Henry Borsook, Ph.D., M.S., Paul Dougherty, M.D., A. A. Gould, M.D. and E. D. Kremers, M.D.
THE VITAMIN C. CONTENT OF CERTIFIED MILK AT THE TIME OF CONSUMPTION	Fred V. West, Dr. P. H. and Joseph C. Wenger, B.S.
CYST OF GASTRO-COLIC OMENTUM	David B. Fishback, M.D.
THE EARLY DIAGNOSIS OF NON-TROPICAL SPRUE, WITH A NOTE UPON ITS FAMILIAL INCIDENCE	G. Louis Weller, Jr., M.D.
AN UNUSUAL CASE OF CHRONIC DUODENAL ULCER	William Fitch Cheney, M.D.
A CASE OF ULCERATIVE COLITIS WITH UNUSUAL COMPLICATIONS	H. N. Taube, M.D.

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12:30 P. M.—Round Table Luncheon Conference.

* * *

2 P. M.—Scientific Session—Italian Room.

Review of the Literature of 1937: Dr. Homer I. Silvers, Atlantic City.

* * *

Symposium on Prolapse:

Compression Ligature for Prolapse of Colostomy (Case Report): Dr. Rufus C. Alley, Lexington.

Treatment of Massive Prolapse by Elastic Ligature—A Criticism: Dr. Mark L. Emerson, Oakland.

A New Surgical Technique for Correcting Rectal Prolapse: Dr. Alfred John Murieta, Los Angeles.

Discussion of Symposium: Dr. Frank C. Yeomans, New York City, Dr. A. J. Chisholm, Denver, Dr. Herbert T. Hayes, Houston.

* * *

Chancroidal Ulceration—Report of Specific Diagnostic Test and Specific Therapy: Doctor Tom E. Smith, Dallas.

Discussion: Dr. E. Jay Clemmons, Los Angeles, Dr. Walter A. Black, Portland, Dr. Curtice Rosser, Dallas.

Pyoderma Simulating Extensive Anal Fistula: Dr. Newton D. Smith, Rochester, Minn.

Discussion: Dr. Clement J. DeBere, Chicago, Dr. Arthur C. Crookall, Seattle, Dr. Edward G. Martin, Detroit.

SUNDAY

11 A. M.—Leave St. Francis Hotel for Drive, Luncheon, Cocktail Party.

MONDAY

9 A. M.

Proctologic Reminiscence:

Three Decades of Proctology: Dr. Alfred J. Zobel, San Francisco.

The Art of Illustration in the History of Proctology (Scientific Exhibit at A. M. A.): Dr. Malcolm R. Hill, Los Angeles.

The Joseph Matthews Address: Dr. Granville S. Hanes, Louisville.

Discussion: Dr. William H. Kiger, Los Angeles, Dr. Frank G. Runyon, Reading, Dr. Collier F. Martin, Philadelphia.

Therapeutic Radiation for Pruritus Ani: Dr. Herbert I. Kallet, Detroit.

Discussion: Dr. W. W. Green, Toledo, Dr. Victor K. Allen, Tulsa, Dr. V. G. Jeurink, Denver.

The Curability of Chronic Ulcerative Colitis: Dr. Montague S. Woolf, San Francisco.

Discussion: Dr. Newton D. Smith, Rochester, Dr. R. Russell Best, Omaha, Dr. Alfred B. Wilcox, Santa Barbara.

AnoRectal Tuberculosis: Drs. A. M. Martin Marino, Alfred M. Buda and Isaac Skir, Brooklyn.

Discussion: Dr. Karl Zimmerman, Pittsburgh, Dr. Hugh Beaton, Ft. Worth, Dr. R. A. Scarborough, San Francisco.

12 Noon—Luncheon.

1:30 P. M.

Multiple Primary Carcinomata of Rectum and Sigmoid Colon: Dr. Harry E. Bacon, Philadelphia.

Discussion: Dr. Thomas E. Jones, Cleveland, Dr. Harry Z. Hibshman, Philadelphia, Dr. William H. Daniel, Los Angeles.

Questionable Proctologic Problems: Dr. Marion C. Pruitt, Atlanta.

Discussion: Dr. Edward G. Martin, Detroit, Dr. Martin S. Kleckner, Allentown, Dr. Cecil D. Gaston, Birmingham.

The Importance of Low Spinal Anesthesia in Proctologic Operations: Dr. Martin S. Kleckner, Allentown.

Discussion: Dr. Walter A. Fansler, Minneapolis.

The Relief of Intractable Pain Due to Inoperable Rectal Cancer: Dr. Howard C. Naffziger, Professor of Surgery, University of California Medical School, President American College of Surgeons, San Francisco (by invitation) and Dr. Howard A. Brown, Assistant Professor of Clinical Surgery, University of California Medical School, San Francisco (by invitation).

* * *

Annual Executive Meeting (Fellows Only).

* * *

7 P. M.—Annual Proctologic Society Dinner. Italian Room.

TUESDAY

Operative Clinics (Morning).

WEDNESDAY

7 P. M.—Annual Dinner of Section on Gastro-enterology and Proctology, Italian Room, St. Francis Hotel. Ladies Invited. (Tickets may be secured from the Secretary).

Abstracts

HEPLER, O. E. AND SIMONDS, J. P.

Mechanism of Shock: Effects of Intravenous Injection of Salt Solution in Collapse Induced by Mechanical Impounding of Blood in the Splanchnic Region in Normal and in Hyperthyroid Dogs. Arch. Path., 25:2-149, Feb., 1938.

The authors start with the fundamental principle that the pathologic process in shock is the impounding of a large volume of stagnant or slowly flowing blood in dilated capillaries in some specific region or more diffusely throughout the body. This process results in the reduction in the volume of the circulating blood, the loss of fluid from the blood, an increase in its concentration, and an anoxemia of the tissues and organs in which the blood is impounded. Because of this shunting of a portion of the circulating blood into the dilated vessels the heart does not receive enough blood to maintain a normal systemic pressure. As attempts to increase the volume of the circulating blood by intravenous injection of fluids is usually of temporary value and as the mechanism of these processes is little understood, the authors studied the problem from experiments in which warm physiologic salt solution was injected intravenously into dogs in which a part of the blood volume had been impounded by mechanically constricting the hepatic veins after the method of Simonds and Brandes. These experiments afforded them the following observations.

When blood is impounded in the liver and gastro-intestinal tract by constricting the hepatic veins the systemic blood pressure falls immediately by 25 to 70 per cent and remains thus for at least thirty minutes.

Injection of physiologic salt solution during the period of constriction of the veins in quantities up to or more than the estimated original blood volume causes a rise in pressure during the period of injection, but it falls again within one to three minutes after the injection is stopped.

The blood volume after injection and while the constriction is on is usually a little greater than the original estimated initial volume plus the salt solution injected. Blood volumes similarly computed after release of the constriction were always much lower.

The rate in fall of blood pressure and reduction in blood volume after injection of salt solution under the conditions of these experiments indicate the rapidity with which fluid escapes from the circulating blood when a considerable part of its total volume is impounded in a known region of the body.

A surprising amount of fluid was found to have escaped into the lumen of the stomach and into the gastric



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submucosa. The peritoneal cavity contained relatively little fluid, the retroperitoneal tissues and the walls of the gall bladder and small intestine were moderately edematous.

Thyrotoxicosis caused a variation in the blood pressures from those noted in the normal dogs. The pressures were lower to begin with, fell to a lower point after completion of the injection, and did not rise as high after release of the constriction on the hepatic veins.

N. W. Jones, Portland.

BOYD; JULIAN D.

Changing Concepts of Normal Nutrition. Northwest Medicine, 37:71-75, March, 1938.

It is the author's opinion that suboptimal states of nutrition are widespread in this country, due to the types of food customarily eaten. He discusses more specifically vitamin D and mineral requirements as related to bone mineralization and tooth decay, and normal vitamin A requirements. This is especially important during childhood, since many characteristics of the

adult body are determined on the basis of adequacy of nutrition during the period of growth. Such nutritional deficiencies do not become obvious until the status of groups receiving prevalent diets is compared with that of those under a wisely supervised nutritional regimen. Then it becomes apparent that states of inferior physique, minor disturbances of health and some types of disease are most frequently dependent primarily on suboptimal diets, and may be prevented or corrected through qualitative and quantitative control of the constituents of the diet. Hanes M. Fowler, Fort Wayne.

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CONNOTATIONS

By H. J. SIMS, M.D., Denver, Colorado

Fabrieus in 1592, published his first surgical work. It was named: "The Pentateuch (five books) Of Surgery."

Leriche called attention to the sympathetic nerve plexuses which are said to lie in the intimate sheath of the large arteries and specified that certain definite results follow excision of these structures. The removal of the structures was designated by him "sympathectomy" and was actually accomplished by his teacher, Jaboulay in 1883.

Hartley of New York, was long attributed as having removed the gasserian ganglion. Foote of Cincinnati, in 1869, carried out the same procedure.

Dr. Joseph Guillotin in 1789, proposed that execution should be free from torture. He devised a machine known as the guillotine. Oddly, this name is given to a number of modern surgical instruments because of the principle of their mechanism.

Osteochondritis of the vertebral body was first described by Calve in 1924.

Glossitis Rhombica, a benign disease of the tongue, was described by Brocq and Pautrier in 1914.

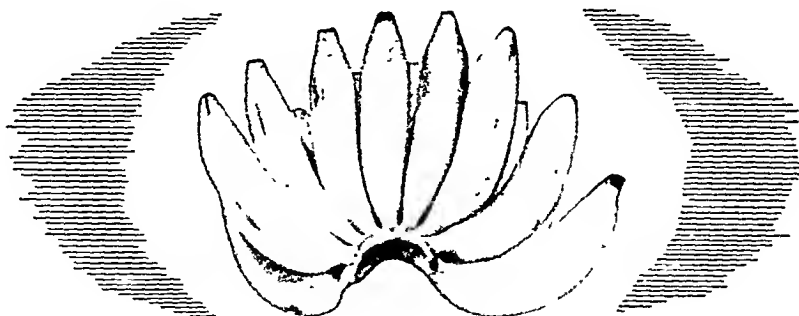
Guthrie in 1934, devised a urethrotomy for incision of the bladder neck. In 1874, Bottini proposed that the obstruction should be incised by the cautery and devised such an instrument.

The Royal College of Surgeons of England have on exhibition a mummified liver with gall bladder calculi. It is a specimen of a priestess of Amenon of the XXI Dynasty (about 1500 B.C.).

Griffin in 1912, reviewed 650 cases of diaphragmatic hernia, only fifteen were recognized before death. In a series of sixty operated cases, recorded by Harrington, the preoperative diagnosis was confused with cholecystitis in 29 cases; gastric disease in 23 cases; and in 7 instances, heart disease.

Seabolew in 1902, first suggested that the pancreas of new-born calves would prove to be the source of internal secretion. Schafer in 1916, proposed the name of insulin.

Laenneck in 1806, described the forms of melanomata in man. Moore in



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1857, described melanoma of the rectum. Such tumors have long been known to occur in animals.

Reclus in 1883, recognized cystic disease of the breast which he termed: "maladie kystique de la mamelle."

Gibson and Malet in 1879, described a case of cleft sternum.

Zenker in 1862, described a case of fat embolism occurring in man.

Seabangew in 1895, attempted to remove an embolus from the femoral artery.

Ardakoff in 1876, was the first to report that the blood of a burned animal was toxic to healthy animals.

Langerhans discovered the islands in the pancreas which bear his name in

1867. Laguesse in 1893, first suspected they produced an internal secretion.

Mering and Minkowski in 1889, removed the pancreas of a dog and taught the cause of diabetes.

Pertussis disease was first described by Legg of Baltimore, in 1909.

Monro in 1797, described a case of myomata of the esophagus.

Jellinek in 1929, described two instances in which bone trauma resulted from electric shock. Burrows of London has recently described a fracture of the head of the humerus, following a shock from 50 cycles alternating current of 230 volts.

Pare in 1610, and Fabricius Hildonus in 1646, each reported two cases of

traumatic diaphragmatic hernia. The first congenital case was reported by Lazars in 1689. Guthrie in 1888, proposed laparotomy for reducing a diaphragmatic hernia.

CONNOTATIONS

By

H. J. SIMS, M.D.

DENVER, COLORADO

Traumatic intrathoracic rupture of the thoracic duct was reported by Bartolet in 1663. Quinke, in 1875, gave an authentic description.

The first omentopexy for portal obstruction with ascites was performed by Van Meulen in 1899 at the suggestion of Talma. The patient died of shock. Morrison, in the same year unknowingly repeated the same procedure with results.

Gould, in 1855, performed one of the earliest jejunostomies for feeding purposes on a patient suffering from carcinoma of the pylorus. The operation was performed under a carbolic spray. The wound was dressed with salicylic wool.

Willett, in 1876; Heath, in 1879; Bull, in 1885, and McGill, in 1866, unsuccessfully attempted to suture a ruptured bladder. McCormack, in 1869, published a report of two successful instances.

In 1833, Myer gave a description of the carotid body and pointed out its common situation at the bifurcation of the carotid artery.

Intracranial calcification is rarely encountered. Heuer and Dandy found only seven cases reported up to 1916, and these by foreign observers.

Complete excision of the scapula was attempted by Lagenbeck in 1855.

Cardamus, in 1556, advocated that people hopelessly immoral should be transfused with blood of those strongly immoral. Evidently, blood transfusion was practiced at this time.

Dr. Werdt of Hamburg, in 1552, disguised himself as a woman to witness the birth of a child. He was recognized and burned alive. Childbirth at this time was in the hands of women of low caste. The aid of priests or men possessed of mystic powers was sought only in difficult cases.

Sir Astley Cooper, in 1829, recognized tuberculosis of the breast. He described the microscopic features as a "scrofulous swelling of the bosom." Dunbar, in 1881, recognized the microscopic features of the disease.

Lieutaud, in 1779, is thought to have recognized a disease now known as linitis plastica. Andral, 1829, attempted to describe the lesion, and to him is credited the report of the first case. Since recognition of the condition, more than forty names have been used to designate its description.

Orthmann, in 1888, first described

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primary carcinoma of the fallopian tubes.

Volkman, in 1822, described contracture of the muscles of the leg in a sixteen year old boy, following application of a splint and a compression bandage. He believed arterial obstruction the principal causative factor. Murphy, in 1914, from experimental work, concluded such a condition was a result of venous obstruction. He stated, "The lesion in Volkmann's contracture is a surgeon's lesion and never a lesion due to trauma." Two years later, he reported a typical instance of Volkmann's contracture, in which no bandages or constrictors were used.

BROOKE, BANNER R.

Colonic and Rectal Cancer. Northwest Medicine, 37:81-83, March, 1938.

The author cites figures to substantiate his conclusion that the incidence of colonic and rectal cancer has increased during the past 15 years or so. He also stresses the importance of early recognition of the condition.

The incidence of rectal and colonic cancers is about equal, with about half as many located in the right side as in the left side of the colon. Gastric disorder, early tumefaction, and early cachexia are prominent symptoms of right-sided malignancy. Obstruction, partial or complete, and hordorgismus are found more often in left-sided cancer, but seldom in rectal cancer. Bright blood in the stool must always be regarded as possible cancer. Sigmoidoscopy and colon roentgenogram should be demanded at once. These procedures should be repeated, if the bleeding persists, until its site has been determined.

The public must be informed of these early symptoms even at the risk of increasing cancerphobia and neurosis. The profession must be more alert in the early identification of colonic and rectal cancer.

Hanes M. Fowler, Fort Wayne.

MANVILLE, IRA A.

Topical Applications of Cod Liver Oil in Treatment of Ulcerative Colitis. Northwest Medicine, 37:75-77, March, 1938.

The author reports a method of applying cod liver oil directly to the mucosa of the sigmoid and rectum by means of a spray nozzle inserted through a sigmoidoscope. He states that the few cases he has so treated for ulcerative colitis have been distinctly benefitted and he cites another report of beneficial results by the same type of treatment. A diagram accompanies the report explaining the construction and use of the apparatus.

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REFERENCES

1. "Treatment of Human Pellagra with Nicotinic Acid"—Fouts, Holmes, Lepovsky and Jukes; *Proc. Soc. Exp. Biol. & Med.*, 37:102, Nov., 1937.
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7. "Pellagra and Nicotinic Acid" as editorial; *J. A. M. A.*, 110:223, Jan. 22, 1938.

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In commercial canning practice, certain operations—specifically the blanch—may aid in elimination of gases from raw food tissues. However, main dependence is placed upon what are known as “exhausting” or “preheating” operations, not only to expel gases from raw foods, but also to exclude air from the can.

Briefly, the exhausting operation is accomplished by mechanically passing the open can containing the raw food through a so-called “exhaust box” in which hot water or steam is used to expand the food by heat and drive out air and other gases contained in the food and in the can. The

times and temperatures used in commercial exhausting operations will naturally vary with the nature of the product (1).

After exhausting, the can is immediately permanently sealed, heat processed and cooled. During cooling, the contraction of the heated contents of the can creates the vacuum normally present in commercially canned foods.

With certain products, instead of exhausting as described above, the same effect is produced by preheating the food in kettles or similar devices; filling into the cans while still hot; and immediately sealing the containers. With still other products, an exhausting effect is produced by adding boiling water, syrup or brines to the food in the can. In some instances, exhausting is accomplished by mechanical rather than by thermal means. Specially designed sealing or “closing” machines are used to withdraw air and other gases by applying high vacuum to the can and immediately sealing on the cover.

Such in brief are the purposes of commercial exhausting operations and the means by which they are usually accomplished. Modern canners recognize that these operations are most important to the success of their canning procedures. They appreciate that only by strict supervision and control of exhausting operations can the quality and nutritive values of their products be maintained at a consistently high level.

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A. W. Bittorf, The Trade-Previews,
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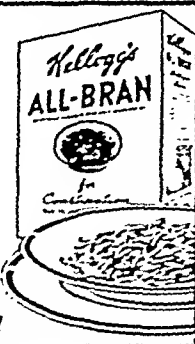
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CONNOTATIONS. By H. J. Sims, Denver, Colo.

Many writers credit Petit with reporting the first case of eventration of the diaphragm. It is frequently stated in literature that Petit recorded his case in 1790. However, Petit died on April 20, 1750. The name eventration was given to the disease by Beclard who was mentioned in the writings of Cruveilhier. Marsh, in 1867, reported the first instance of its clinical recognition with autopsy findings.

Cruveilhier, in 1829, accurately described a cranial epidermoid, although Leprestre and Dupuytren had previously described similar neoplasms. In 1838, Johannes Muller contributed an excellent monograph on this subject.

Little first visualized the possibilities of colostomy after observing in an infant a congenital division of the rectum. Such a procedure was carried out by Pillare, in 1776.

Bernays was the first in America to successfully remove the entire stomach. In 1894, he performed the first cesarean section for placenta previa.

The use of zinc peroxide as an antiseptic dressing was suggested by Ellias, in 1903.

Hippocrates recognized and described ischiorectal abscesses. Celsus, 400 years later, advised the use of the knife in the treatment of fistula. One thousand years after Hippocrates' observation, Paul of Aigina, not only described fistulas and their complications, but offered principles in their surgical treatment which is now recognized.

Dugas sign (L. A. Dugas, 1806-1884) "If the fingers of the injured limb can be placed by the patient upon the sound shoulder while the elbow touches the thorax, there can be no dislocation, and if this cannot be done, there must be a dislocation."

Extradural nonparasitic cyst of the midthoracic region was recognized by Schlesinger, in 1898.

Sir Astley Cooper, in 1829, described tuberculous disease of the breast as a "serofulous swelling of the bosom." Virchow believes the breast immune to tuberculosis. Lancereaux, in 1860, was the first to establish the diagnosis by microscopic examination. Cuneo, in 1868, isolated the organism from the pus and successfully inoculated an animal with it.

In 1888, Anton and Fütterer isolated the *B. typhosus* from the gall bladders of fatal typhoid fever cases.

CONNOTATIONS. By H. J. Sims, Denver, Colo.

The rapid formation of renal calculi following injury to the spinal cord was first commented upon by Costello, in 1833. He stated Earle had previously described several cases of lithiasis attributable to injuries in the lumbar region. In 1835, Muller stated that in approximately 10 per cent of the cases of fracture of the vertebrae when accompanied by paralytic symptoms result in formation of kidney stones.

Aufrecht, in 1850, reported a case of primary myoma of the right saphenous vein originating in the region of the internal malleolus. Boettcher, in 1867, reported a similar case involving the ulnar vein.

Duodenal ulcer following external burns has often been reported in the literature, the first description being by Long, in 1810, and by Curling, in 1842.

A higher incidence of Osgood-Schlatter's disease has been reported among the Japanese. Kato suggested that the increased incidence is a result of frequent kneeling.

Hodges, in 1880, coined the term "piloid" sinus from the Latin *pilus*, meaning hair, and *nidus*, meaning nest. He believed the lesion to be due to invaginations of hairs in the postnatal fold. Warren, in 1867, probably recognized this anomaly and suggested that it be a result of change in growth of the hair follicles in the sacral region.

Aberrant pancreatic tissue was recognized by Klob, in 1859. Zenker, in 1861, attributed it to the formation of an additional pancreatic bud from the foregut which developed as an independent mass which had been carried away from its point of origin.

Lateral dislocation of the wrist is apparently rare. Ore



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of the first recorded cases was mentioned in the Bulletin de la Société de Chirurgie de Paris, in 1874. Another instance was noted in a manuscript on Fractures and Dislocations by Hamilton, published in 1884.

Cystic hygroma of the neck is a rare condition. Arnold, in 1865, concluded that a congenital defect represented the underlying cause.

Struma lymphomatosa, a rare type of abnormality of the thyroid gland was first described by Hashimoto, in 1912.

Piedel, in 1883, described a peculiar inflammatory condition of the thyroid gland which led to the formation of an iron-hard tumor. Twelve years later he observed a second case and in 1896, he published his observations of the disease to which he gave the name *eisenharte Strumitis*. Bowey noted a similar case, in 1885, and described it as a fibrating fibroma.

OPPENHEIMER, G. D.

Recurrent or Residual Progressive Ileitis. J. A. M. A., 110:1103, April 2, 1938.

The author reports the case of a 28 year old Jewish man who on January 18, 1928, was admitted to the hospital with the complaint of colicky abdominal pain unrelated to meals and of three weeks duration. On the day of admission the pains became more severe and localized in the right lower quadrant. Clinically the condition was considered an abscess of the appendix. Laparotomy was done, the appendix removed and the area drained. The convalescence was stormy, the temperature being 107.6° F. on the first post-operative day, but he was discharged on the twenty-first day.

Eight months later the scar broke down, drained a purulent material, and then healed spontaneously. On May 5, 1931, the patient was readmitted with the complaint of pain over the scar for the past two weeks. The temperature was 103° and there was a fluctuant mass beneath the scar. This was incised, pus evacuated and three days later fecal drainage was noted. Iodized oil was injected and revealed a fistula communicating with the cecum. The patient was then discharged with moderate fecal drainage. On July 31 he was readmitted but conservative measures were decided upon and he was again discharged.

On October 27 he was again admitted with the complaint of weight loss, febrile episodes, and abdominal pain for the past month. The fistula was still present and was studied with X-ray and iodized oil. Laparotomy was done, the ileum and 12 cm. of the ascending colon were resected and an isoperistaltic ileotransverse colonic anastomosis was done. Pathological examination of this revealed hyper-trophic chronic ulcerative inflammation of the colon.

Follow-up showed the patient to be well until June, 1936, when he developed watery stools and epigastric pain. Operation was again performed on November 7, 1936, and an ileosigmoidal side to side isoperistaltic anastomosis was done. To date the patient is carrying on as a normal individual.

From these results the author thinks it is not possible to differentiate between a residual and recurrent lesion and that when resection is done the ileum should be divided at least 8 to 12 inches proximal to palpable or visible involvement. In addition the operator should examine the ileum carefully far above the lesion so as not to skip an involved area.

Francis D. Murphy, Milwaukee.

LIDLAW, GEORGE F.

Nesidioblastoma, the Islet Tumor of the Pancreas. Amer. Jour. Path., XIV, 2:125, March, 1938.

The author gives a microscopic study of 9 "adenomas of the islets of Langerhans" removed surgically from 6 patients. Clinically it is of interest because these tumors

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were removed for the relief of hypoglycemia with severe and long continued collateral symptoms of from 1 to 12 years duration. All of the patients recovered from the operation. In 5 of the 6 patients operated upon the blood sugar rose and the collateral symptoms disappeared promptly. In one case the removal of a tumor failed to give improvement, but at a second operation one month later another tumor was found and removed, which resulted in prompt recovery of the patient.

The tumors were small, from 4 mm. to 2 cm. in diameter. In the larger tumors there was extensive fibrosis and calcification. Hyaline degeneration was also noted. Structurally they resembled gigantic islets of Langerhans. They duplicated the pattern of normal islets. They arose from the duct epithelium of the gland. According to Bensley and others the duct epithelium of the pancreas is the source of all growth and repair. In the embryo, as shown by Bensley, epithelial buds from the duodenum grow toward the spleen as branching pancreatic ducts. This duct epithelium is totipotent: i.e., at one point it differentiates into acinous cells, at another point into islet cells, and at other points it pushes forward as branching ducts. This property of the duct epithelium is retained throughout life, and upon it depends the remarkable instances of complete regeneration of the pancreas as a whole, as has been observed in the adult rabbit (Grauer). Once differentiated out of the duct epithelium the islets grow by proliferation of their own cells (Bensley).

The islet tumors may be regarded as a reaction of the duct epithelium to a stimulus that has called forth its duct-building and islet-building potencies, leaving the acinous-building potency in abeyance.

The name nesidioblastoma is proposed in order to give specific identification to these tumors as well as to avoid the more cumbersome designation of adenoma of the islets of Langerhans. Selecting the Greek word for islet, the cells which differentiate out of the duct epithelium to build islets may be called nesidioblasts-islet builders, and when they form tumors the latter may be termed nesidioblastoma. As there is some evidence of a diffuse or disseminated proliferation of the islet cells as a possible cause of hypoglycemia, carrying the application of the name further, it would be logical to designate such diffuse proliferation of nesidioblasts nesidioblastosis.

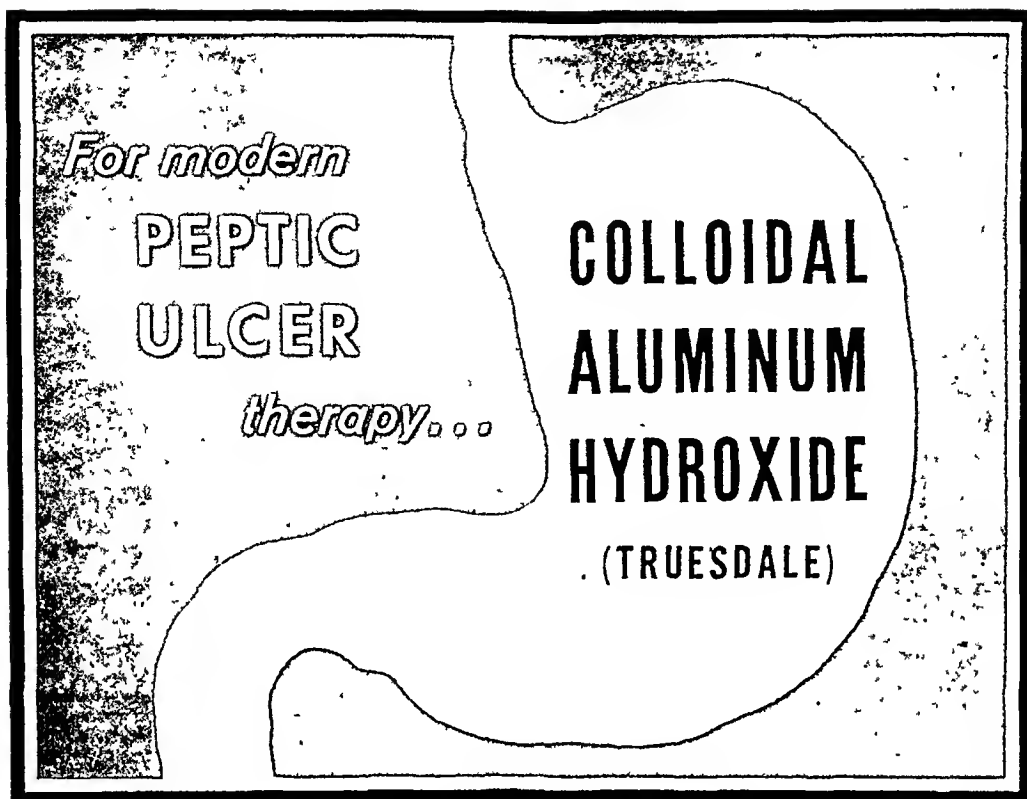
N. W. Jones, Portland.

HARTUNG, C. A. AND WARKANY, J.

Duodenal Ulcer as a Cause of Death in a Case of Meningococcic Meningitis. J. A. M. A., 110:1101, April 2, 1928.

Ulcer of the duodenum frequently occurs in childhood. In early life it usually occurs in the new born suffering from melena neonatorum and in marantic infants. In later childhood ulcer is the result of trauma, burns, nephritis, uremia and infections. Ulcers due to infection include those associated with tuberculosis, syphilis, typhoid, pneumonia, small pox, chicken pox, scarlet fever, diphtheria, measles, erysipelas, pemphigus and appendicitis. It has never been reported, however, in association with meningococcus meningitis. The authors report the case of a negro boy who came under their care. The entrance complaint was pain in the chest and abdomen. The admission temperature was 101.4°. The evening after admission he had a convulsion and the next day the neck became rigid. Kernig's sign was positive, spinal puncture revealed a pressure of 20 mm. and a cell count of 5000 per cubic millimeter. Culture of the spinal fluid was positive for meningococci. The patient was treated with antimeningococcus serum and he appeared to be improving. He suddenly developed slight tremors of the body. A soap-and-water enema was returned with a large amount of soft brown fecal matter. He died within two hours. Autopsy revealed a duodenal ulcer, sections of which showed gram-negative diplococci similar to those found in the meninges.

Francis D. Murphy, Milwaukee.



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The Process of Intestinal Rotation in the Human Being Illustrated by the Dried Intestines of the Cat

By
E. G. WAKEFIELD, M.D.,* C. STUART WELCH, M.D.†
and
CHARLES W. MAYO, M.D.‡
ROCHESTER, MINNESOTA

FOR the sake of description, rotation of the human intestine during embryonic development has been divided into three stages. Models to illustrate each of these stages of intestinal rotation would necessarily be somewhat diagrammatic. However, we have been able to prepare dried specimens of the intestines of cats by maintaining the desired anatomic relations of the intestines during drying. These aid greatly in visualizing the important steps of the interesting phases of development of the intestines.

In a 7.5 mm. human embryo the umbilical loop of the intestine has been formed and is herniated into the umbilical cord. Herniation into the umbilical cord is the result of intra-abdominal pressure and the increasing length of the intestine. Examination of the contents of the umbilical hernia shows that the small intestine from the jejunum to the proximal colon is contained in the umbilical cord. This section of the intestines is freely movable on its dorsal primitive mesentery, as shown by the first specimen on the left in Fig. 1. This specimen shows a fixation of the duodenum and colon, which is the result of shortening and thickening of the mesentery at these points. The duodenum and colon are thus brought into close approximation. This approximation is known as the duo-

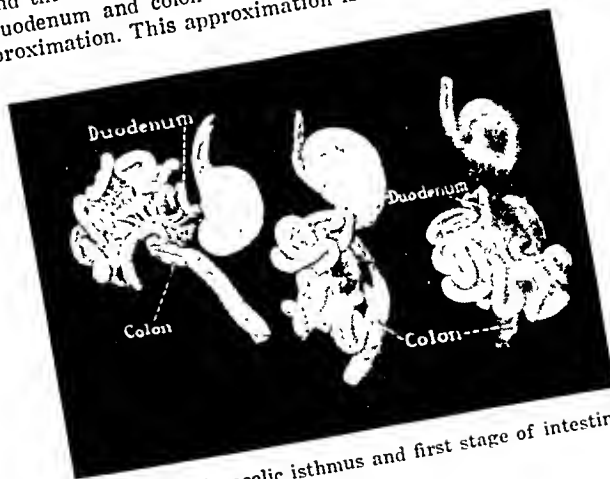


Fig. 1. Duodenocolic isthmus and first stage of intestinal rotation.

denocolic isthmus. It is about this point that intestinal rotation normally takes place or abnormally fails. In order to understand intestinal rotation, the relations of the duodenum and colon at the extremities of these

mesenteric fixations must be closely visualized at each stage of development. The center specimen in Fig. 1 is a ventral view of the first specimen.

By the time the embryo is 10 mm. in length, the umbilical loop has turned about 90 degrees counter-clockwise from a sagittal to a horizontal plane. This

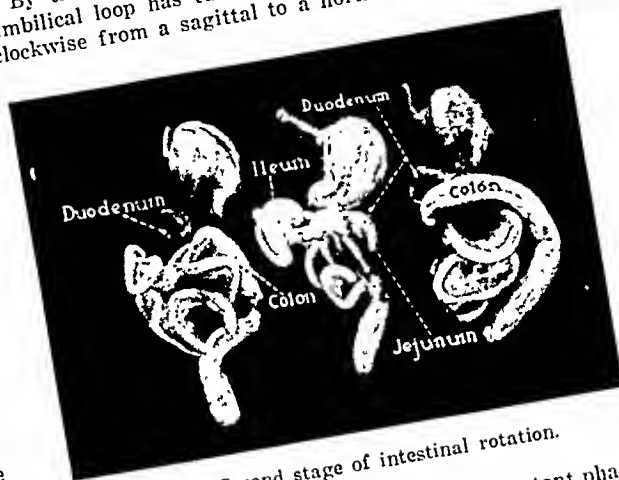


Fig. 2. Second stage of intestinal rotation.

turning of 90 degrees accomplishes an important phase of rotation which is designated as the first stage of rotation. In this specimen, the cecum and proximal colon are ventral to the duodenum before rotation, whereas, in the specimen on the right, the proximal portion of the colon and the cecum are now on the same level as the duodenum and proximal portion of the jejunum and in a horizontal plane, which now is the plane of the duodenocolic isthmus.

In the second stage of rotation the intestine returns to the abdomen. The mechanism of this return is purely physical, and the intestine is literally sucked back into the abdomen. There are a decrease in the rate of growth of the liver, an increase in the resistance in the umbilical hernia, which is caused by the ever enlarging intestine, pressure of the amniotic fluid outside the hernial sac and a collapse of the lower part of the abdominal wall, all of which combine to produce the "sucking-back" process.

In this stage it is obviously impossible for the intestine to return en masse. The best evidence favors the view that the jejunum (specimen on the left in Fig. 2) begins to pass back and is followed by the ileum and, finally, by the colon. Mall observed that the small intestine is back in the abdomen while the colon and the terminal portion of the ileum are still in

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Submitted October 18, 1937.



Fig. 1. X-ray appearance of stomach and duodenum. Note the deformity in the pyloric region and duodenal bulb. (Case No. 1)

which will undoubtedly have a far-reaching effect on our present concept of the diagnosis, prognosis and treatment of gastric disease.

The revelations of gastroscopic studies have been increasingly enlightening in various diseases of the stomach, but probably the most noteworthy contributions have been in the diagnosis of gastritis.

For years, chronic gastritis has been cloaked in mystery; accepted by some and denied by others as being a true pathological condition. In the past some of our standard medical text-books have either relegated it to a place of insignificance or ignored it entirely.

Today, however, to deny the existence of chronic gastritis as a definite disease entity would be as erroneous as stating that gastric ulcer or gastric carcinoma did not exist. The work of Hurst (3), Schindler and Ortmyer (4), Faber (5), Konjetzny (6) and others proves conclusively that chronic gastritis must be added to our nomenclature of gastric disease. Eusterman (7), in a recent publication on the Gastritis Problem presents conclusively established cases of gastritis, in which the diagnoses were confirmed at necropsy by histologic examination of surgically excised or resected tissue or by combined clinical and gastroscopic, or by roentgenologic findings. An interesting aspect of his report deals with ten cases of sub-acute or chronic gastritis in which operation was performed. The pre-operative studies of the stomach indicated organic disease such as polyps, ulcer or carcinoma; yet the operative and histologic data disclosed only sub-acute or chronic gastritis. In his report there is no evidence to indicate that these patients had been gastroscoped before operation, and Eusterman concludes that, obviously, the solution of the gastritis problem depends chiefly on gastroscopy.

There were many classifications of gastritis before the advent of gastroscopic studies, but since then, the simplest scientific arrangement has been proposed by Schindler (4) who divides chronic gastritis into four groups: 1—Superficial; 2—Hypertrophic; 3—Atrophic; 4—Post-operative.

The gastroscopic appearance of these various types of chronic gastritis has been fully described in previous communications by Schindler and others.

Gastroscopically, it has been observed that there is a close relationship between atrophic gastritis, pernicious anemia, polypoid and malignant lesions of the stomach. It is not uncommon to find atrophic gastritis and polyps in cases of pernicious anemia, and the malignant degeneration of polyps is not infrequent. In cases of pernicious anemia, with atrophic gastritis, Jones, Benedict and Hampton (8) have observed gastroscopically a regeneration of the mucosa after adequate liver therapy.

Turning to the problem of gastric ulcer and its generally conceded tendency to become malignant, we are again confronted with inconsistent evidence. Data based upon voluminous statistics obtained from large clinics would indicate that five to as high as thirty-five per cent of gastric ulcers become malignant. Where can one find solace in this morbidity? The most comforting answer to this question would seem to be found in Schindler's (9) gastroscopic observations of gastric ulcer. In over one hundred cases of true gastric ulcer he has not observed one to become malignant.

From the standpoint of differential diagnosis we have unhesitatingly employed gastroscopy whenever indicated (10). The presentation of three cases with unusual aspects seems justified in an attempt to stimulate greater interest in this relatively new field of objective science.

Case 1. Mr. C. D., a real estate broker, forty-two years of age, referred by Dr. Sidney Cousins, complained of a gnawing epigastric pain. The pain occurred about one hour after meals and had been recurring intermittently for fourteen years. Food or alkali had given immediate, though temporary, relief. There had been some nausea and vomiting of blood. There was anorexia and weakness but no weight loss. Physical examination revealed under-nutrition of eighteen pounds. Gastric analysis—free HCl 50°, total acidity 70°, Wasserman and Kahn test negative. He brought with him the following roentgenologic report (Fig. 1).



Fig. 2. Showing circumscribed area of rarefaction in the duodenal cap. (Case No. 2)



Fig. 3. Re-examination of stomach and duodenum showing absence of area of rarefaction in the duodenal cap. (Case No. 2)

"The stomach shows very marked hyperperistalsis and there is a large deforming lesion of the pyloric region involving both the pylorus and cap, which does not produce obstruction. This is probably due to an ulcer, but lues and early malignancy must be considered. It is suggested that the stomach be re-examined in a brief period." One week later, we have the following report: "Re-examination of the stomach shows a definite ulcer of the duodenal cap. There is an inflexible infiltration along the greater and lesser curvatures of the pylorus for a distance of about three centimeters. This may be due to scar tissue, but the possibility of an early malignancy is great enough that an exploratory operation is advised." At gastroscopy ten days later the following was observed: "The antrum was best seen in the four o'clock position, which was most unusual, indicating that the pylorus was not free to fall anteriorly. This unusual lack of mobility probably signifies a fixation of the pylorus or duodenum by peri-pyloric adhesions. No peristalsis was observed in the antrum. Distal to the musculus sphincter antri on the greater curvature was a fairly good sized bolus of thick grayish white tenacious mucus. This pathological mucus was adherent in spots to the antral mucosa near the pylorus, but with each respiration it seemed to separate in web-like fashion. There was another small fleck of yellowish-white mucus adherent to the musculus sphincter antri. At first it gave the impression of a little deeper shade than that normally seen. The mucosa appeared to be more edematous than hypertrophied and, at times, had some aspects of stalactites, but not true polypoid in character. This left no

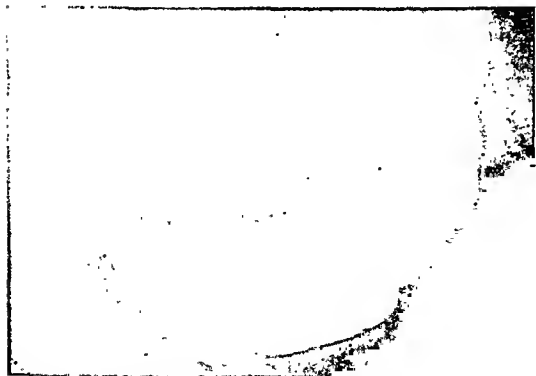


Fig. 4. Appearance of duodenal cap eleven days after first examination. (Case No. 2)

doubt that a moderate degree of superficial gastritis of the antrum was present. No new growth could be observed. Proximal to the angulus there appeared to be a cup-shaped depression of the mucosa which may have represented some redundancy of the mucosa in this area, but not a true diverticulum. This could account for the slight out-pouching seen on the lesser curvature with the X-ray. In the mucus lake no bloody mucus was observed, but most of it was of a moderately thick consistency containing bubbles.

Gastroscopic Impression: Peri-pyloric and peri-duodenal adhesions preventing proper rotation anteriorly of the stomach with the patient in the left lateral position. Superficial gastritis of the antrum." On the basis of this report, the patient was not subjected to operation but treated medically for duodenal ulcer. A communication discloses that this patient has entirely recovered.

Case 2. Mrs. W. T., twenty-eight years of age, housewife. Referred by Dr. Karl Corley. On May 1, 1937, the patient had several tarry stools and complained of weakness and dizziness. The physical examination was negative except for generalized pallor. Haemoglobin was 51% and R.B.C.'s 2,700,000. The surgical consultant made a provisional diagnosis of duodenal ulcer, Meckel's diverticulum, or carcinoma or benign tumor of the cecum. On May 10, ten days later, the first X-ray report was as follows: (Fig. 2) "The esophagus and stomach are normal. There is a circumscribed area of rarefaction in the duodenal cap, which suggests a benign lesion, probably polyp." Two days later: (Fig. 3) "Re-examination of the stomach and cap shows no evidence of abnormality of the cap, but duodenal polypi have their origin in the mucous membrane of the stomach and may protrude through the pyloric sphincter or may not, which accounts for its appearance at one examination and not at another." From this report it was evident that surgical exploration was indicated, but before this was done, gastroscopy was requested. The gastroscopic report was as follows: "The antrum was well seen and the pyloric opening was easily identified. The mucosa appeared normal in all respects.



Fig. 5. X-ray appearance of stomach and duodenum. (Case No. 3)

There was no abnormality in the body of the stomach or in the fundus." One week later the patient was re-examined with the X-ray by another roentgenologist who reported as follows: (Fig. 4) "Fluoroscopic examination of the stomach is negative. The duodenal bulb is regular. There is a slight irregularity of the second portion of the duodenum. The possibility of this being an ulcer should be considered." The patient apparently has recovered. The final diagnosis was not verified by operation, but it is presumed that she was suffering from hemorrhage from a duodenal ulcer.

Case 3. Mr. C. P., fifty-five years of age, carpenter by occupation. Admitted to Emergency Hospital March 29, 1937. This patient gave a two-year history of intermittent severe epigastric pain following the taking of food. There was slight loss of weight and strength. The physical examination was essentially negative. The abdomen was flat and soft without masses or tenderness. Haemoglobin was 54%, R.B.C.'s 2,940,000. Gastric analysis, without using the Alcohol test meal and Histamine, revealed absence of free HCl and a total acid of 35, with microscopic blood present. Examination of the feces, using the Benzidine Test for occult blood, was positive ++. The X-ray report was as follows: (Fig. 5) "Fluoroscopic examination of the chest and esophagus negative. There is no evidence of disease of the stomach or duodenum. There is a sensory resistance just below the greater curvature which was very suggestive of a lesion of the pancreas." Fifteen days

after admission to the hospital the patient was discharged with the following working diagnosis: possible carcinoma of the stomach, possible carcinoma of the pancreas, possible peptic ulcer. Ten days later, April 22, 1937, the patient was re-admitted to the hospital for gastroscopy which revealed a rather large friable hemorrhagic carcinoma on the anterior wall and greater curvature of the stomach. One week later abdominal operation was performed and an inoperable malignant mass was found on the anterior wall and greater curvature of the stomach. Nineteen days later the patient died. At necropsy a section of the mass revealed an adenocarcinoma, grade three, papillary type.

COMMENT

From these case reports one would naturally assume that one method of study was more decisive than the other. However, this is the exception rather than the rule as X-ray and gastroscopy should supplement each other and should not be viewed as competitive branches of science. This is especially true where there is a divergence of opinion as to the differential diagnosis. I would, furthermore, caution against over-enthusiasm in this new field of observation, as only by a conservative attitude and careful study of each case, together with accurate correlation of all data obtained, can the merit and value of gastroscopy be appreciated.

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A Simple Test for Determining the Presence of Gastro-Intestinal Lesions A Preliminary Report

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THERE are a good many occasions when the physician feels the need of a simple test to determine the presence or absence of a gastro-intestinal lesion. The patient may be so ill that roentgenographic study is impossible or contraindicated because of bleeding or possible perforation. In instances in which radiograms can be made, the evidence they furnish is not always conclusive, for healed lesions with scar formation, or deformities due to a spastic duodenum can not always be distinguished from active lesions. The availability of a simple procedure of this type would also aid in differentiating between organic and functional disease of the gastro-intestinal tract, and between gastro-intestinal disease and diseases outside the digestive system which display symptoms referable to the stomach or intestine.

It was the inability of the roentgenologist to state positively whether the deformity observable in the roentgenogram of a patient who had received treatment for peptic ulcer indicated a healed or an active

lesion which recently led me to search for a procedure which might give more accurate information in these doubtful cases.

It seemed rational to assume that a non-toxic substance which is not normally absorbed through the mucous membrane of the digestive tract, but which might enter the circulation through any break in the mucosa with eventual excretion in the urine, would be suitable for this purpose.

After preliminary investigation, it appeared that phenolphthalein might prove of value in such studies. This drug has been used widely as a mild laxative, and has been the subject of experimental investigation by numerous workers. All of these are agreed that practically 90 per cent of the phenolphthalein is excreted almost immediately with the feces. Vamossy (1) believes that the small quantity of phenolphthalein absorbed is converted into a conjugate, probably a sulpho-compound. In a series of 650 cases in which a small medicinal dose of phenolphthalein has been taken by mouth, Fantus and Dyniewicz (2) have found that free phenolphthalein is generally absent in the urine,

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but that conjugate phenolphthalein is always present. They also observed that with larger doses, a greater proportion of patients display free phenolphthalein in the urine, and the quantity of conjugate phenolphthalein is correspondingly increased. Abel and Rowntree

TABLE I

Results of the phenolphthalein test in patients with gastro-intestinal lesions

Diagnosis	Cases	Result	
		Positive	Negative
Duodenal ulcer	17	16	1
Gastric ulcer	3	3	0
Hematemesis	4	4	0
Carcinoma of stomach	6	6	0
Carcinoma of colon	3	3	0
Ulcerative colitis	2	2	0
Total	35	34	1

(3) showed that phenolphthalein is not absorbed by the small intestine in dogs, but that there was evidence of slight absorption by the large intestine.

Since phenolphthalein is widely used as a chemical indicator, its detection in the urine, even in minute quantities, is a very simple procedure. Phenolphthalein produces a pink or red color in alkaline solutions, and hence its presence, in dilutions as high as one to ten millions, is plainly shown by the addition of alkali to the urine.

Phenolphthalein is non-toxic, even in large doses, and there is no other contraindication for its use. The few untoward reactions which have been reported have been of allergic type in hypersensitive individuals (4, 1).

For the purposes of this test, it is advisable to administer the phenolphthalein in solution, and in a quantity small enough not to produce a laxative effect, nor to be capable of detection in the urine of normal individuals. Phenolphthalein is not soluble in water, but is readily dissolved in 95 per cent alcohol (5). Even if the alcohol is slightly diluted with water, it will stay in solution, but it will precipitate out in a 20 per cent alcohol-water mixture. For this test, 1 gram of white phenolphthalein is dissolved in 100 c.c. of 95 per cent alcohol. The dose administered is 10 c.c. of this solution, or 0.1 gram of phenolphthalein.

The procedure is as follows: The patient drinks 10 c.c. of the 1 per cent solution of phenolphthalein in alcohol, diluted to 30 c.c. by the addition of water. The water is added to give a larger volume of liquid in the stomach, and to make the solution more palatable, by reducing the strength of the alcohol. The solution should be administered in the morning, when the patient is in a fasting state, because food may prevent the solution from reaching the lesion in the gastro-intestinal mucosa. If the stomach is full of water, the solution might become too dilute, or the phenolphthalein might precipitate out, and hence not reach the break in the mucous membrane. The patient is instructed not to eat or drink for one hour after taking the phenolphthalein.

Specimens of urine are obtained two and four hours

after the patient has taken the phenolphthalein solution. In some instances a six-hour specimen may also be necessary, in case the patient has some condition which may delay the appearance of the drug, such as acute or chronic nephritis, cardiac failure, fever or dehydration.

A portion of each specimen of urine is poured into two containers, one to be used for comparison of color with the other portion, to which 10 per cent sodium hydroxide solution is added. The best containers for the specimens are white porcelain evaporating dishes or small beakers placed on white paper. Test tubes are not satisfactory for these color comparisons, for there is not enough depth to the fluid in them to bring out the color. The 10 per cent solution of sodium hydroxide is added with a dropper until no more change in color takes place. Occasionally a precipitate is formed when the alkali is added, because of the presence of earthy phosphates which are insoluble in alkaline solution.

The urine must be examined promptly, for otherwise false positives may be obtained. As Fantus and Dynciewicz (2) have shown, conjugate phenolphthalein is always present in the urine of a person who has taken phenolphthalein. This does not yield a pink color on the addition of alkali, but if the urine is allowed to stand, some chemical action takes place, probably through bacterial activity, which liberates free phenolphthalein and produces the characteristic reaction.

The test should not be repeated for several days, as phenolphthalein can be detected in some instances forty-eight or seventy-two hours after ingestion. If a

TABLE II

Results of the phenolphthalein test in patients without gastro-intestinal lesions

Diagnosis	Cases	Result	
		Positive	Negative
Normal persons	31	0	31
Gall bladder disease	11	0	11
Cardiovascular disease	9	0	9
Diabetes	3	0	3
Arthritis	8	0	8
Asthma	4	0	4
Renal calculus	2	0	2
Morphine addict	1	0	1
Healed ulcer	6	0	6
Coronary thrombosis	1	1	0
Multiple sclerosis	1	1	0
Total	77	2	75

repetition of the test is desired, a specimen of urine should be tested before an additional quantity of phenolphthalein is administered.

CLINICAL STUDY

It was necessary to prove that the phenolphthalein does actually pass into the circulation through any break in the continuity of the mucous membrane, because of an ulcer or a malignant growth, and then is excreted with the urine in sufficient quantity to be

detectable on the addition of sodium hydroxide solution. We had an opportunity to demonstrate this on a patient who had a carcinoma in his mouth on the lower jaw. A piece of cotton was saturated with the solution of phenolphthalein and placed on the lesion in his mouth for one hour. The patient was instructed not to swallow any of the solution. Phenolphthalein was present in the urine at the end of four hours. A normal person who had no break in the mucous membrane in the mouth was subjected to the same test, without any evidence of phenolphthalein in the urine at the end of four hours. Several days later, the patient with the carcinoma in his mouth was asked to drink the phenolphthalein solution through a straw so that it would not come in contact with the lesion. The urine was examined two and four hours afterward, and no evidence of phenolphthalein was found.

This test has been performed on 112 subjects. Seventy-seven were individuals who had no apparent gastro-intestinal lesion, and thirty-five had gastro-intestinal lesions demonstrated roentgenologically or by other means.

Of the 35 patients with lesions, all but one showed a positive test for phenolphthalein in the urine (Table I). In the exceptional instance, there was radiographic evidence of an irregular duodenal cap, and the patient had pain one-half hour after meals which was relieved by food but not by alkalis. Since the last finding is atypical for duodenal ulcer, the patient may not have had an active lesion. The case is listed with the cases of gastro-intestinal disease, because of the roentgenographic picture.

Of the 77 cases with no apparent gastro-intestinal lesion, 75 exhibited no evidence of phenolphthalein in the urine after two and four hours. Two patients in this group displayed free phenolphthalein in the urine (Table II). This control series included 31 normal persons in good health (internes, nurses and colleagues) and 46 patients, both ambulatory and hospitalized, who had some disease other than that of the gastro-intestinal tract. The hospital patients were used because it was felt that they would furnish data which could be compared fairly with those obtained in the group of patients with peptic ulcer or carcinoma of the gastro-intestinal tract. The two patients in this control group in whom tests for free phenolphthalein in the urine were positive were both too ill to check thoroughly for the presence or absence of a gastro-intestinal lesion. One had advanced multiple sclerosis, and the other coronary thrombosis. The latter died a few days after the test was made, but post-mortem examination was refused. It is possible, of course, that these patients may have had some lesion in the stomach or intestines which was not suspected or was masked on account of the other disease present, but this has not been proved.

Several cases in this study deserve special comment. One patient, F. H., male, aged 62 years, had a mass in his epigastrium. The roentgenologist's diagnosis was "retroperitoneal tumor probably in the pancreas, which causes a pressure defect on the lesser curvature of the stomach." In this case, the phenolphthalein test was strongly positive. The patient died and a post-mortem examination revealed an adenocarcinoma of the stomach.

Another man, J. L., aged 60 years, was in the hospital with a carotid sinus syndrome. A very poor history

was obtained because of the patient's inability to speak English. The phenolphthalein test was positive. After this, he was sent to the X-ray department for gastro-intestinal study, where a diagnosis of duodenal ulcer was made, confirming the results of the phenolphthalein test in a patient in whom a gastro-intestinal lesion had been unsuspected.

A patient of Dr. E. D. Cumming, G. W., female, aged 56 years, had an hour-glass stomach which was thought to be due to an ulcerative lesion caused by either a gastric ulcer or a gastric carcinoma. The phenolphthalein test was negative after two hours, four hours and six hours. The following day an exploratory laparotomy revealed a fibrous band which encircled the stomach causing a marked constriction. This band was cut and the constriction immediately disappeared. No evidence was found of an ulcer or carcinoma.

Many urine specimens which contained no free phenolphthalein at the end of four hours, did show its presence after standing 24 hours. This no doubt was due to the splitting off of free phenolphthalein from the conjugate form. Additional evidence of this reaction was observed in several other specimens in which a pink color was obtained on the addition of a 10 per cent solution of sodium hydroxide at the end of the test period, but yielded a deep red color with alkali after standing 24 hours.

In the series of tests here described, only qualitative estimations have been recorded, which seems to indicate, in a small series, a high degree of reliability in determining the presence or absence of a lesion in the gastro-intestinal tract. At the present time, more extended studies are in process to attempt quantitative estimations, since there is some evidence that the quantity of phenolphthalein excreted may have a relation to the size of the lesion. These studies will be the subject of a later report.

SUMMARY AND CONCLUSIONS

A simple test is described for determining the presence of a break in the continuity of the gastro-intestinal mucous membrane. This is accomplished by the administration of 0.1 gram of phenolphthalein in alcohol solution, which is easily detectable, if present in the urine, by the addition of 10 per cent sodium hydroxide two or four hours after ingestion of the test solution. If the test is positive for free phenolphthalein, a break in the mucous membrane of the gastro-intestinal tract caused by ulcer or carcinoma is indicated. If the test is negative, it indicates that the mucous membrane is intact.

In a series of 112 cases, the possible error has been less than 3 per cent both for positive and negative findings.

The reliability of the test depends on the small quantity of phenolphthalein used, and prompt examination of the urine specimens. If these conditions are disregarded, false positives may be obtained.

Phenolphthalein is an ideal drug for this purpose because it is non-toxic, is easily taken by any patient in the small quantity required, and without laxative effect, and the technic for its qualitative estimation in the urine is extremely simple.

The test has a wide field of usefulness in those cases in which roentgenographic evidence is of doubtful authenticity, in differentiating between functional and

organic disease, and in ruling out organic lesions of the gastro-intestinal tract in diseases which may have symptoms referable to the digestive system.

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The Effects of Acetylcholine, Acetylbetamethylcholine and Prostigmine on the Secretion of the Stomach of Man and Dog

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WHILE choline has no effect (1), some of its esters have pronounced effects on gastric secretion. Surprisingly, the results of various investigators are widely diverging. In 1930, Allodi (2) and Reggiani (3, with a test meal) found that acetylcholine (a.c.) raised gastric secretions. Bagnaresi in 1931 (4) reported that a.c. increased volume secretion distinctly and acid secretion less markedly. Faroy and Deron (5) stated that unlike histamine, a.c. when injected daily for prolonged periods, eventually raised the secretion of acid in clinical cases of an- and hypo-acidity, and recommended a.c. for the treatment of these conditions.

In 1932, Wilkinson (6) reported that a.c. when given with a test meal raised the secretion of free HCl in normal human subjects. In 1933, Abbott (7) found increased free acidity in 6 out of 9 normal human subjects and in some patients with achlorhydria following a test meal and acetylbetamethylcholine chloride (a.m.c.). Gebhardt and Klein (8)

tory observed increased acid secretion with a.m.c. and Destree (12) made the same observation with carbaminylcholin (dogs). Recently Schnedorf and Ivy (13) reported that a.m.c. induced acid secretion of the stomach of monkeys refractory to histamine. In most of the tests referred to above, the choline esters were given subcutaneously but in some, intravenously or, in larger doses, per os; one experimenter gave a.c. in suppositories, besides (8).

Our experiments were begun in 1935 before we knew of Myerson's work, and the results presented below tend to explain the divergence of results in this field.

METHODS

Five dogs with Heidenhain pouches were employed. Four were males and one was a female; their body weight ranged between 12 and 20 kg. All of them were in excellent health. The animals were fasted for 24 hours before the tests. The human subjects were normal adults, without gastro-intestinal or other complaints. They fasted for 14 hours before the tests. Levine tubes were passed through the mouth and the stomach contents were aspirated, measured, and all but 10 c.c. returned into the stomach, except in the case of the first aspiration, which was not reinjected. All drugs were given subcutaneously.* Free and total acid were titrated against dimethylaminoazobenzene (method of Michaelis), and phenolphthalein, using n/10 NaOH; acidity is expressed in clinical units, (i.e., cems. of n/10 NaOH required to neutralize 100 cems. of gastric juice). Peptic activity was estimated by the modified Mett method and expressed as the product of Mett units and volume of secretion (14).

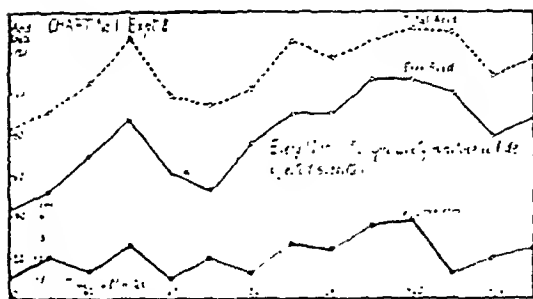
RESULTS

I. On Dogs.

The data in Table I prove that a.c. chloride, a.c. iodide, a.m.c. chloride and prostigmine definitely raise the acid secretion of the Heidenhain pouch.

A. Acetylcholine (Chart 1).

A.C. is the weakest stimulant among the drugs employed; 100 mgm. had very little effect (expt. No. 1) but 400 mgm. induced distinct rises of volume and



published that a.c. raised the acid secretion of the stomach in only a few of their normal subjects. In 1935, Ferguson and Smith (9) reported that, following a test meal, small doses of a.m.c. increased and larger doses of a.m.c. diminished the secretion of free acid in monkeys. In 1936, Myerson, Rinkel and Dameshek (10) published their results on patients with dementia praecox. Using a.m.c. they found decrease or disappearance of gastric acid secretion and even acid deficit. In 1937, Gray (11) from Ivy's labora-

*From the Department of Gastro-Intestinal Research of Michael Reese Hospital, Chicago. Aided by the Oscar Aberle and Otto Baer Funds.

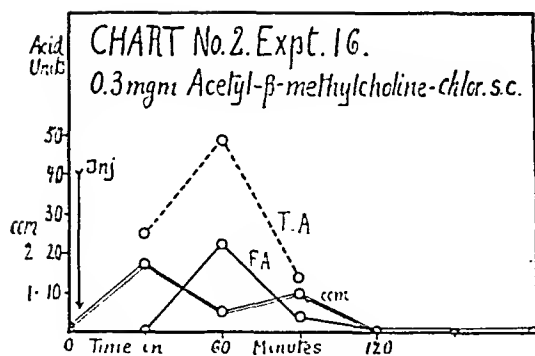
*Acetylcholinechloride and Prostigmine supplied by Hoffman-La Roche. Acetylbetamethylcholinechloride (Methochyl) supplied by Merck & Company.

acidity (expt. No. 2). The effect lasted for 60 minutes after the injection. Repeated injections of 10-100 mg. of a.c. given every 10 minutes (except in expt. No. 9, every 30 minutes) regularly evoked considerable secretion of acid (expts. 3-9, and Chart 1). In the case of a single dose, the maximum effect of the drug was at-

tained 30 minutes after injection and with repeated doses (which individually were, of course, smaller than the single doses) 30-90 minutes after the beginning of injections. In some experiments two peaks were observed (No. 8 and 9). In one experiment (No. 6) the increased secretion following the first injection

TABLE I
Effect of subcutaneous injections of choline esters on pouch secretion

Expt. No.	Dog No.	Injections			Changes From Control Values to Maximum Responses			Period in Minutes Between Inj. and Max. Response		Return to Control Values, Min. After Last Inj.	Remarks
		Dose of Each Inj. in Mg.	Number of Inject.	Period Between Inj. in Min.	Volume c.c.	Free Acid in M.E.	Total Acid in M.E.	Volume	Acidity		
A. Acetylcholinchloride and Acetylcholiniodide*											
1	12	100	1		Trace to 1.1	0 to trace	to 20	30	30	60	
2	12	400	1		0.1 to 1.3	Trace to 34	to 52	30	30	60	
3	52	10	12	10	Trace to 3.8	0 to 40	to 60	50	60	90	
4	4t	10	7	10	Trace to 1.5 3.5 to 27 Nett Units	Trace to 40	to 96	75 60	90	40	
5	12	20	9	10	.1 to 2.9	Trace to 26	to 41	80	86	130	
6	52	20	15	10	Trace to 3.5	0 to 10	to 25	30	30		During inj. period gradual drop of vol. and free ac. to control values
7	44a	50	6	10	Trace to 0.8	0 to 67	to 100	60	60		
	b	100	3	10	0.8 to 1.0	67 to 20	100 to 40	30	30	120	90 min. after last inj. values rose to approx. max. of 44a
8	41	50*	40	10	2.5 3.8	67 106	135 132	90 300	90 300		Response slightly irreg. 2 peaks (at 90 and 300 min.). This dog had practically no basal secretion
9	52	50*	14	30	2.0 2.4	25 41	58 59	30 390	30 390		2 peaks (at 30 and 390 min.) drop to low values between peaks
B. Prostigmine (P) and Acetylcholine Chloride (A)											
10	52	P. 1.0	1		Trace to 3.8	0 to 50	to 79	30	60	210	
11	12	P. 0.25 A. 12.5	1		Trace to 2.0	0	4	90	90		Volume did not drop to control values
12	44	P. 1.0 A. 50.0	1		Trace to 3.3	0 to 70	to 88	60	60	150	
C. Acetylbetamethylcholine											
13	44	.1	1		No effect						
14	44	.3	6	30	Trace to 2.0	4 to 45	to 92	15	130		
15	44	.5	6	30	Trace to 3.2	0 to 90	to 100	20	50		
16	52	.3	1		Trace to 1.7	0 to 22	to 49	30	60	120	
17	52	5.0	1		to 1.8	Trace to 32	5 to 59	90	120	150	
18	52	20.0	1		.5 to 1.3	0 to 44	22 to 88	150	120		Not back to cont. val. 150 min. after inject.
19	52	.5	6	30	to 5.0	to 71	to 88	30	30		Slight drop, and 2nd maximum at 150 minutes
20	12	.5	1		Trace to 1.6	0 to 3	to 12	30	60	90	Old somewhat refractory Heidenhain Pouch
21	12	1.0	1		Trace to 2.8	0 to 17	to 27	50	60	90	
22	12	10.0	1		Trace to 1.4	0 to 9	to 25	60	50	120	
23	12	30.0	1		.3 to 1.0	0 to trace	9 to 32	30	150		Did not return
24	12	1.0	7	30	to 4.0	to 50	to 72	30	60		Slight drop after 120 minutes

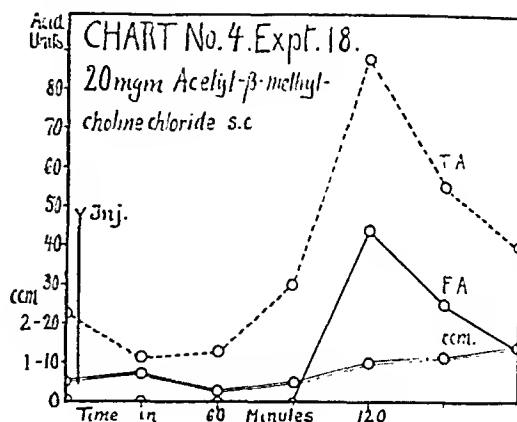


of a.c. was not maintained, although 20 mgms. of a.c. was injected every 10 minutes, and the values dropped to zero. Generally it can be said that injections of a.c. in repeated doses at regular intervals raised acid secretion considerably, but did not maintain a steady level of secretion as histamine, or a.m.c. frequently do. This is understandable because the effect of histamine and a.m.c. depends essentially on the rate of absorption, while that of a.c. depends both, on the rate of absorption, and the rate of destruction by esterase. In 8 out of 10 experiments the maximum of volume and of acid secretion occurred simultaneously (a 30 minute difference in No. 3 and a 15 minute difference in No. 4). A.C. definitely increased the secretion of pepsin (experiment No. 4). The question whether stomach secretion to a.c. can be maintained without exhaustion of the secretory mechanism has been answered by experiments No. 8 and 9 (see Chart 1). In both experiments secretion remained elevated for 6½ hours with subcutaneous injections of a.c. iodide repeated every 10 and 30 minutes, respectively.

B. Prostigmine and A.C.

Prostigmine (1 mgm.) very definitely raised volume and acid secretion (experiment No. 10). The peak of volume secretion was reached 30 minutes before that of acid secretion. Duration and degree of secretion were considerable when compared to the effects of a.c. and of a.m.c. on the same dog (No. 52).

Since prostigmine delays the destruction of a.c. these two drugs were combined (expts. No. 11 and 12). Because from previous experience on dogs (and from tests on man carried out at present) we knew the potentiating effect of the two drugs (15), very small doses of a.c. were employed. One mgm. of prostigmine

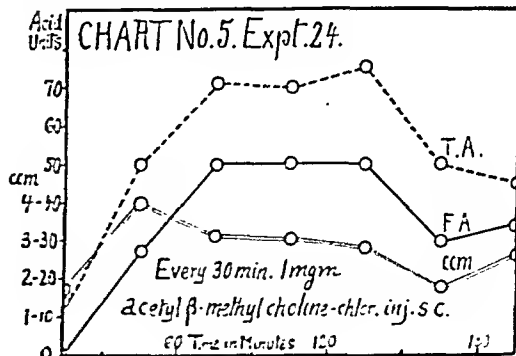
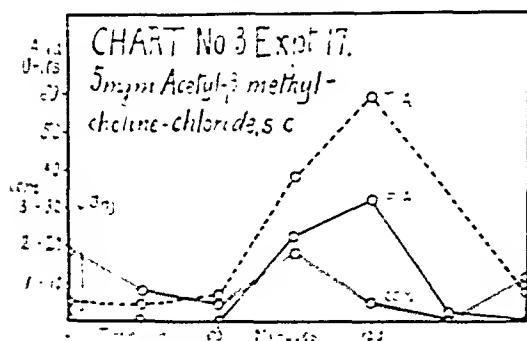


and 50 gammas of a.c. raised volume and acidity of pouch secretion considerably, and the peak values for both were attained simultaneously.

C. Acetylbetamethylcholine chloride (Charts 2-5).

The smallest dose of a.m.c. employed, namely .1 mgm. had no effect (expt. No. 13), but doses of .3 mgm. and upward raised volume and acidity of secretion. Repeated doses of a.m.c. had very pronounced effects and all secretions of the stomach rose distinctly (expts. No. 14, 15, 19 and 24). There is an interesting difference between the effect of a.c. and that of a.m.c. While with a.c. the maximum secretion of fluid and of acid was attained simultaneously in most experiments, a dissociation of the two was observed in the case of a.m.c. (see Table I and Charts 2-5). In nine out of eleven experiments volume secretion reached its maximum earlier than acid secretion. The retardation of the peak of acid secretion varied between 15 and 150 minutes, but was 30 minutes in 7 out of 9 experiments. Since the gastric secretion was collected every 20 minutes, the dissociation must have taken place during this period; a few observations showed that the peak of volume secretion was attained at the beginning of this period. No clear relationship was found between the dose of a.m.c. and this phenomenon.

Do increasing doses of a.m.c. depress the secretion of the pouch as described by Gray (11)? In order to answer this question the results with a.m.c. in Table I have been grouped according to individual dogs. Comparing the results for total acidity in each dog we notice that it rises definitely with increasing doses of

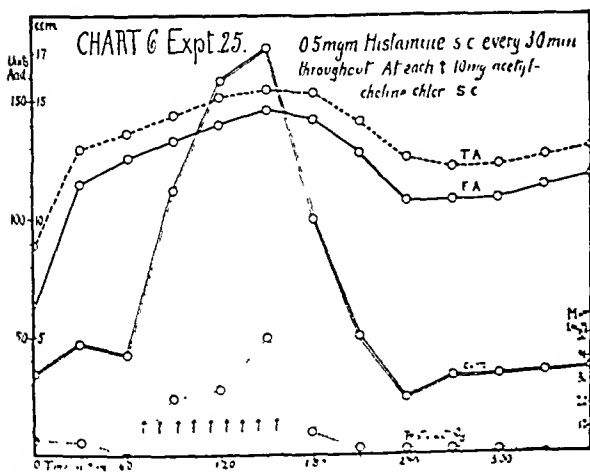


a.m.c. Comparing the period of time elapsing between injection of a single dose of a.m.c. and the maximum response of acidity we see that the secretion of acid is delayed, or "postponed" by a.m.c., and that this delay is greater with larger doses of a.m.c. (see Charts 2-4). The total secretion of HCl (in mgms.) for a period of 3 hours after the injection of a.m.c. was the following: In dog No. 52, single doses of 0.3, 5.0 and 20.0 mgms. of a.m.c. evoked a secretion of 2.9, 4.2 and 8.4 mgms. of HCl, and in dog No. 12, 0.4, 1.0, 10.0 and 30.0 mgms. of a.m.c. evoked a secretion of 1.2, 1.5, 1.7 and 2.3 mgms. of HCl. Dog No. 12 had an old (two years) and somewhat refractory Heidenhain pouch. These data show that the secretion of HCl by the Heidenhain pouch is greater with larger doses of a.m.c. and that the effect of the larger doses amounts to a delay but not suppression of acid secretion. Chart 5 demonstrates that repeated doses of 1.0 mg. of a.m.c. do not exhaust acid and volume secretion of a pouch over a period of 3 hours (see also expts. No. 14, 15, 19 and 24).

In order to investigate the interaction between choline esters and histamine and pilocarpine, the following experiments were done on Heidenhain pouch dogs:

I. The Effect of A.C. on Pouch Secretion Provoked by Histamine* (Chart 6, Expt. No. 25†).

0.5 mgm. of Histamine was injected subcutaneously every 30 minutes for a period of six hours. Following a control period of 90 minutes, 10 mg. of a.c. were injected subcutaneously every 10 minutes for 90 minutes. From Chart 6 it is evident that the addition of a.c. to histamine raised acid secretion slightly, but fluid secretion to nearly four-fold its control level. It increased also the secretion of pepsin which, as has been shown by Babkin and collaborators, is not stimulated in the dog by histamine, and which had dropped to nearly zero in the control period in which only histamine was injected; this was probably due to the "washing out" effect assumed by Babkin (16). Pepsin secretion rose to nearly 50 units under the influence of a.c. and then dropped to practically zero when histamine alone was continued. Following the cessation of a.c. injection, volume and acidity fell below the control level and recovered gradually towards the end of the experiment. In an identical experiment (No. 26) on

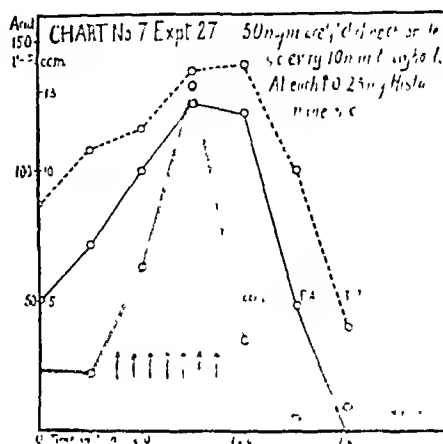


*Ergamine acid phosphate used throughout.
†From here on the experiments are not listed on tables.

dog No. 52, the same results were obtained except that the rise in volume was not so great (from 2.8 to 10.0 ccms.) and that its depression after cessation of a.c. injections was much greater (from 12.4 ccms. to 4.8 ccms. with consequent recovery to 7.0 ccms.).

II. The Effect of Histamine on Pouch Secretion Provoked by A.C. (Chart 7, Expt. No. 27).

In the following the experimental procedure was reversed and the effect of histamine on a secretion provoked and maintained by a.c. was tested. Two such



experiments were made in which 30 and 50 mg. of a.c. respectively were injected subcutaneously every 10 minutes for periods of 5 and 4 hours respectively. Superimposed upon this 0.25 mgm. of histamine was injected every 15 and 10 minutes respectively. The results were essentially the same as in the reverse experiment but the depression of acid secretion following the stopping of histamine injections was more pronounced than in the preceding group of experiments. Volume secretion dropped from the control value of 2.2 ccms. to 0.4 ccms. while the secretion of free acid dropped to zero, although 50 mg. of a.c. were given every 10 minutes (Chart 7, Expt. No. 27). In the other experiment (30 mg. of a.c. every 10 minutes) free acidity dropped from the control level of 70 to 48 C.U.,* total acidity from 100 to 76 C.U., and volume from 0.7 to 0.4 ccms.; 30 minutes later the volume rose to 1.9 ccms. (Expt. No. 28).

III. The Effect of A.C. on Pouch Secretion Provoked by Histamine-Pilocarpine.

Since gastric secretion to a meal corresponds more to the combined effects of histamine and pilocarpine than to the effect of histamine alone (Babkin 16), three experiments were carried out in which 0.5, 0.5 and 1.0 mgm. respectively of histamine plus 0.5 mgm. of pilocarpine† were injected subcutaneously every half hour throughout the entire experiment (Expts. No. 29-31). After a control period, 10 mgms. of a.c. were injected subcutaneously every 10 minutes for 90 minutes, and after that the experiment was continued for approximately four hours with only histamine-pilocarpine. In two experiments the same effects as in the previous group of experiments (histamine without pilocarpine) were noted while in the third experi-

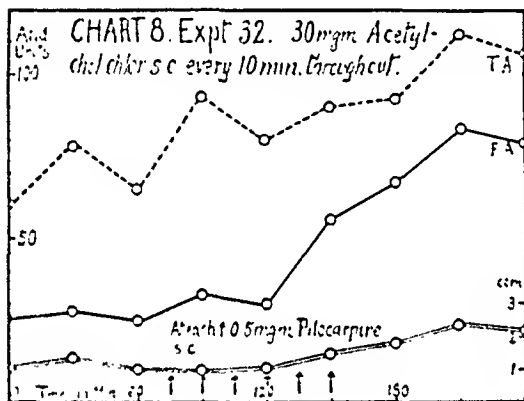
*Clinical units.

†Pilocarpine nitrate was used throughout.

ment volume and acid secretion dropped considerably during and recovered after cessation of a.c. injections.

IV. *The Effect of Pilocarpine on Pouch Secretion
Provoked by A.C. (Chart 8, Expt. No. 321).*

As a control to the above experiments, secretion was provoked by subcutaneous injections of 20 mgms. of a.c. every 10 minutes to which was added, after a control period, 0.5 mgm. of pilocarpine (every 15



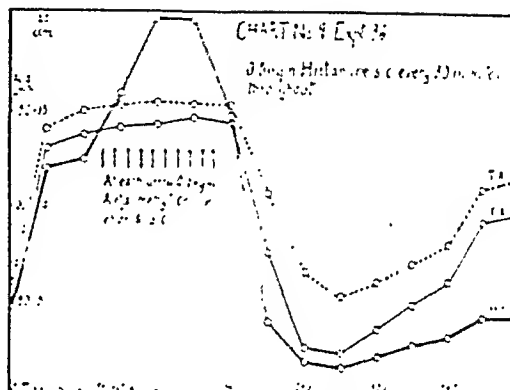
minutes). A great increase in the secretion of free acid and a smaller but yet very evident increase of volume and total acidity followed the injection of pilocarpine and continued after its cessation. The experiment was repeated on the same dog, using 30 mgm. of ac and only 0.25 mgm. of pilocarpine with similar but somewhat less pronounced results, probably due to the smaller dose of pilocarpine (Expt. No. 35). It should be noted that injection of pilocarpine raised free acidity and decreased combined acidity, i.e. probably the secretion of mucus, in experiment No. 32 (see Chart 8) was raised.

V.—*The Effect of A.C. on Pouch Secretion Provoked by Pilocarpine.*

In the following experiments the above procedure was reversed. One mgm. of pilocarpine was injected subcutaneously every 30 minutes and after a control period 30 mgms. of a.c. in addition were injected every 10 minutes for a period of 90 minutes (Expt. No. 34). While pilocarpine itself increased volume secretion only, the addition of a.c. raised secretion of volume and of free and total acid considerably. The effect was maintained for 60 minutes after the last injection of a.c. In the same dog the experiment was repeated, using only 0.5 mgm. of pilocarpine and 10 mgm. of a.c. In this experiment a.c. raised only the volume of secretion while free and total acidity were not changed (Expt. No. 35).

VI. *The Effect of A.M.C. on Purch. Selection Pro-*
posed by Hottelmeier (Chart 9, Expt. No. 36).

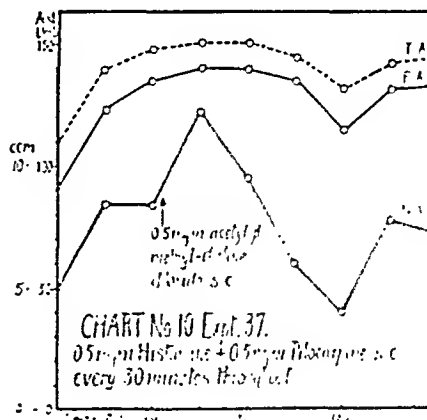
Histamine 0.5 mm. was injected subcutaneously every 30 minutes for 7 h; after constant acid secretion was established 0.1 mm. of a.m.c. was injected subcutaneously every 10 minutes for 90 minutes. A slight rise of acid secretion and a large rise of volume secretion occurred when a.m.c. was superimposed upon histamine. A marked depression of volume and acid



secretion beginning after the stoppage of a.m.c. injections was followed by slow recovery.

VII. *The Effect of A.M.C. on Pouch Secretion Provoked by Histamine-Pilocarpine (Charts 10 and 11, Expts. 37 and 39).*

In order to complete the picture, a single dose of a.m.c. was superimposed upon the effects of constantly repeated injections of histamine-pilocarpine, 0.5, 5.0 and 20.0 and 30.0 mgms. respectively of a.m.c. were given in four different experiments (No. 37-40, the first three on the same dog), in which active pouch secretion was maintained by injections at 30 minute intervals of 0.5 mgm. of histamine and 0.5 mgm. of pilocarpine. 0.5 mgm. of a.m.c. produced a slight rise

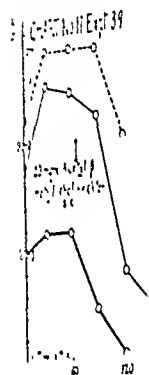
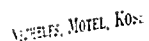


of acidity and a marked rise of volume, both followed by depression and recovery to control levels (Chart 10). 5.0 mgms. of a.m.c. was followed by an immediate drop of acid and volume secretion, the latter being much more marked, with slow recovery to control values; an appreciable intermediary rise of free acidity occurred. 20.0 (Chart 11) and 30.0 mgms. of a.m.c. produced an immediate large drop of volume and acid secretion with slow recovery of fluid secretion and faster recovery of acid secretion to control values.

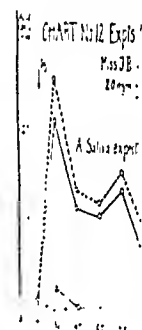
2. *On Men* (Chart 12, Expt. No. 43-44).

A. *Acetylcholinesterase*.

Two sets of experiments were done on one normal



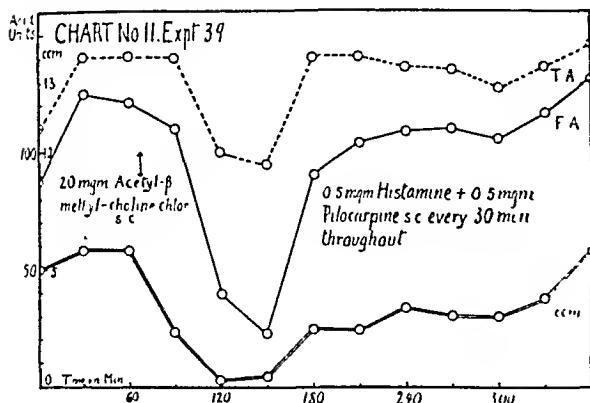
colored male subject (normal white female) taking one dose of 2 g.-m. In one set the in the next one, followed. A great free acidity dropped to and rose considerably



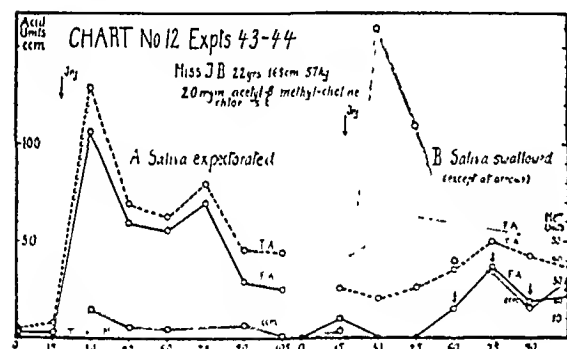
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colored male subject (Expts. No. 41-42), and on one normal white female subject (Expts. No. 43-44) receiving one dose of 20 mgms. a.m.c. in each experiment. In one set the subjects expectorated all saliva, in the next one, done a week later, all saliva was swallowed. A great difference was noted, in so far as free acidity dropped to zero when saliva was swallowed and rose considerably, even in the same experiment,



when it was expectorated. Chart 12 is representative of the results on both persons. The large increase of volume in the second experiment indicates the amount of neutralizing and diluting fluid by swallowed saliva. We realize that in an experiment of longer duration, saliva would act as gastric secretagogue (19). Pepsin secretion was increased by a.m.c.

B. Prostigmine.

After a control period a healthy male subject received a subcutaneous injection of 1 mgm. of prostigmine. All saliva was expectorated. Secretion rose from a control value of 11 ccms. with free acidity of 21 C.U. and total acidity of 38 C.U., to values of 68 ccms. and 43 and 58 C.U. respectively. Peptic activity rose from a control value of 43 Mett units to 173 units. Volume, acidity and peptic activity remained elevated for more than 60 minutes.

DISCUSSION

The question whether a.c., a.m.c. and prostigmine produce an acid or alkaline secretion of the stomach has been definitely answered for the secretion of the Heidenhain pouch and of the normal human subject: a large single dose of a.c. and smaller repeated doses of a.c., small doses (above 0.3 mg.) and larger doses

of a.m.c. (up to 30 mgms.) all produce increased secretion of fluid and of acid by the stomach (subcutaneous injection). Myerson's results on patients (10) in which he obtained alkaline secretion to a.m.e. may be explained by the possible swallowing of much of the saliva, which is secreted so abundantly following injections of choline esters. At least our experiments on human subjects have proved that in the same person a good response of secretion of free and combined acid is obtained when the subject carefully expectorated all saliva, and that when he swallowed it free acid was absent. We realize that our results do not explain why Myerson and collaborators obtained an acid deficit (10), while in our experiments free acidity dropped to zero and some total acid was present. It may be possible, however, that either the salivary or the gastric secretion of the patients employed by the above mentioned group of investigators was different from that of our normal subjects. It seems worth while remarking that Abbot, who found an increase of gastric acid secretion in normal subjects following a.m.c. remarks in his paper that precautions were taken against swallowing of saliva (7, p. 325). In one of Myerson's experiments (10, Chart 3, page 1009), a significant initial rise of free and total acid is apparent after injection of a.m.e.

We confirm Gray's findings (11) of potent stimulation of gastric secretion by small repeated doses of a.m.c. Gray reports that repeated larger doses of a.m.c. (1 mgm.) stimulate the production of a small quantity of an alkaline secretion in dogs with pouches of the whole stomach. Our findings (1 mgm. of a.m.e. given every 30 minutes did not exhaust acid secretion for 3½ hours, see Chart 5 and Table I, No. 24) are not necessarily opposed to his, because we employed Heidenhain pouches. Since it seemed possible, hence, that the alkaline secretion of the pyloric antrum might be increased by a.m.e., we injected one dog with a pyloric pouch (without vagus supply) with 1.0, 3.0 and 5.0 mgms. respectively of a.m.e. subcutaneously (on different days). No increased secretion of the pouch was noted however. Since there are mucus glands in the cardia, fundus and body of the stomach, besides those in the pyloric antrum, the difference between Gray's and our findings cannot be explained at present; besides, it is well conceivable that a whole stomach pouch and a Heidenhain pouch may have different mechanisms of secretion besides a possible difference in mucus production. Other differences between our findings and those of Gray may possibly be explained similarly. Doses of a.m.c. above 1 mg. produced only a small quantity of alkaline secretion in his experiments while we found doses up to 30 mg. (subcutaneously) producing acid secretion of the pouch which in the latter case did not return to control levels 180 minutes after injection (see Table I and Charts 2, 3 and 4).

Large single doses of a.m.c. (up to 30 mgms.) depressed the secretion of a pouch to constantly repeated injections of histamine + pilocarpine, but did not make it refractory to histamine-pilocarpine. For the reasons cited above this finding is not necessarily opposed to that of Gray who, besides, gave repeated injections of 1 mg. of a.m.c. every 10 minutes for two hours and then found the whole stomach pouch refractory to histamine.

Our results with prostigmine on a human subject and on dogs are opposed to those of Myerson and

collaborators (10) on patients. They found that prostigmin produced essentially the same effects on gastric secretion as did a.m.c., i.e. a marked reduction in acidity with increased mucin content; fluid secretion was not changed appreciably. In tests in which physostigmin or prostigmin was followed shortly by a.m.c. they found that prostigmin acted as a synergist to a.m.c. thus enabling small doses of a.m.c. to produce a marked effect in changing the gastric juices from acid to alkaline (10, page 1012). Our experiments (Table I, No. 10-12) on pouch dogs proved to the contrary that prostigmine alone as well as in combination with a.c., effected an unquestionable secretion of fluid, free and total acid, and the experiment on man showed that 1 mg. of prostigmine produced a marked gastric secretion of fluid, pepsin and of acid provided no saliva was swallowed. In view of these findings we would feel reluctant to use these drugs in the treatment of peptic ulcer, as proposed by Myerson, Rinkel and Dameshek (10, p. 1012).

Babkin (16) recommended the use of histamine-pilocarpine for function tests of the stomach, rather than that of histamine only. In view of our results, which demonstrated that a.c. stimulated acid as well as peptic secretion, and that histamine and a.c. act on gastric secretion synergistically, it might be worth while to consider a combination of these two compounds for a function test of the stomach, as well as for the treatment of hypo- and certain an-acidities (see Faroy and Deron, 5). Besides, from the physiological standpoint, a.c. would seem to be a more "normal" stimulus than pilocarpine.

In our experiments with a.m.c. (see Table I) the peak of fluid secretion was attained before that of acid secretion. We have observed the same with histamine frequently, but not regularly. In experiment No. 10 prostigmine acted similarly, but not in combination with a.c. (expts. 11-12). The increase of fluid secretion following a.m.c. usually occurred during the first half hour, and in some experiments we have observed it to begin within 10 minutes after injection.

When comparing results in the same dog it becomes apparent that increasing doses of a.m.c. provoke increased gastric secretory response; but the period of time between injection and onset as well as peak of acid secretion is prolonged with the larger doses of a.m.c.

Histamine (and histamine + pilocarpine) and a.m.c. in small doses (0.5 mgm. subcutaneously) are synergists. Following the synergistic effect a depression of histamine secretion occurs, followed by recovery (see Chart 10). Large doses of a.m.c. depress histamine-pilocarpine secretion temporarily, followed by more or less rapid recovery (see Chart 11). Repeated injections of small doses of a.m.c. (see Chart 9) effected a small rise of acid and a large rise of volume secretion followed by a profound depression of both and slow recovery.

Histamine or histamine-pilocarpine and a.c. are likewise synergists for gastric secretion. In eight experiments in which 10-50 mgms. of a.c. were superimposed

upon histamine stimulated secretion or in which histamine was superimposed upon a.c. stimulated secretion, the output of volume and acid was largely increased, and was depressed upon discontinuation of the superimposed drug, with slow recovery following in most experiments. In only one test did superimposing of a.c. (10 mg. every 10 minutes) depress histamine secretion immediately, with recovery after cessation of a.c. injections.

Pilocarpine does not suppress pouch secretion to a.c. In two experiments pilocarpine superimposed upon a.c. secretion (30 mg. a.c. subcutaneously every 10 minutes) raised volume and acid secretion considerably (see Chart 8). We may therefore say, that a.c. in larger doses raised volume and acid of a pouch secretion produced by pilocarpine. In previous work on man, we have found that pilocarpine decreased gastric secretion of acid (17, see also 1 and 18). We found that in normal persons (but not in ulcer patients) pilocarpine increased secretion of visible mucus. In the Heidenhain pouch pilocarpine seems to be synergistic to a.c. in raising acid secretion. Histamine (or histamine-pilocarpine) and a.c. as well as a.m.c., seem to be synergists when injected together, but a temporary partial exhaustion of the secretory response to one of them becomes apparent when the injection of the second drug is stopped. It must be a peculiar mechanism, worth while of further analysis, by which two gastric secretagogues act as synergists in small doses, followed by secretory depression, when one of them is discontinued. On the other hand a large dose of one drug will suppress a secretion maintained by the other one. A somewhat similar phenomenon has been reported by Alley from Babkin's laboratory (20), in that histamine lowers gastric secretion to sham-feeding and to a meal.

SUMMARY

Acetylcholine increased acid, volume and pepsin secretion of the Heidenhain pouch. It did not exhaust secretion for seven hours, when 50 mgm. of acetylcholine iodide was injected every 10 minutes.

Acetyl-beta-methyl-choline in small and large doses increased acid and volume secretion of the pouch. Large doses effected a preliminary inhibition of secretion followed by a greater secretory response than that to smaller doses.

Acetylcholine and histamine were found to be synergists relative to gastric secretion. A depression of secretion appeared after one of them was discontinued, followed by recovery.

Histamine and small doses of acetyl-beta-methyl-choline acted synergistically on pouch secretion. A depression of secretion and slow recovery followed discontinuation of one of them. Large doses of acetyl-beta-methyl-choline depressed histamine-pilocarpine secretion, but the pouch was not refractory to histamine-pilocarpine. Prostigmine and prostigmine plus acetylcholine produced increased secretion of acid of the Heidenhain pouch.

Acetyl-beta-methyl-choline stimulated gastric secre-

tion of volume, acid, and pepsin in normal subjects. Swallowing of the saliva (plentifully evoked by this drug) lowered free acidity to zero.

Prostigmine stimulated human gastric secretion of fluid and acid. In view of our results regarding the stimulating effects of acetyl-beta-methyl-choline and

prostigmine on the acid secretion of the human stomach, we cannot advise the use of these drugs in the treatment of peptic ulcer as proposed in the literature.

We wish to thank Miss H. Katz and Mr. I. Beylin for technical assistance.

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The Takata Reaction in the Blood Serum*

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IN 1925 the Japanese professor Maki Takata introduced a new differential test of the blood serum which he intended for use in the diagnosis of lobar and lobular pneumonia (1). To 1 cc. amounts of dilutions of serum from 1:5 to 1:500 in a medium alkalized by 0.25 cc. 10% Na_2CO_3 he added 0.25 cc. of a mixture of equal parts of 0.5% HgCl_2 and 0.02% basic fuchsin. After ½ hour in a water bath at 15° C. a positive reaction showed precipitation as well as bluish coloration of the supernatant fluid in the dilutions of 1:10 to 1:70 or 1:100. A positive reaction was said to occur in lobar pneumonia and in some cases of tuberculosis of the exudative type. Collaborating with K. Ara, Takata (2) also employed a modification of this test in the spinal fluid: a blue-violet precipitate occurred in central nervous system syphilis, while a rose coloring of the liquid without precipitate occurred in cases of meningitis.

During the past 12 years both tests have been further investigated by a large number of workers. The publications dealing with the spinal fluid fall outside the scope of this paper. In 1929, Staub and Jezler (3) modified the test of the blood serum slightly, failed to corroborate its occurrence in lobar pneumonia but found that changes occurred in the presence of cirrhosis of the liver. Jezler (4, 5, 6) experimented

extensively with the reaction during the next several years. He used a series of 8 tubes each containing 1 cc. of serum diluted with 0.9% NaCl to make concentrations of 1:2 to 1:256. To each tube was added 0.25 cc. Na_2CO_3 and 0.3 ccm. of reagent, consisting of equal parts of 0.5% HgCl_2 and 0.02% aqueous fuchsin. Readings were made immediately, after ½ hour and after 5 hours. For the occurrence of a positive reaction it was necessary for flocculation to appear in at least 3 tubes, the first of which had a concentration of 1:32 or more. Of approximately 1247 cases done, the diagnosis was checked by autopsy in 264. 70% of 176 cases of cirrhosis of the liver yielded a positive reaction. Among 90 cases of cirrhosis confirmed by autopsy, 80% were positive; among 86 cases diagnosed by clinical criteria only, 58% were positive.

Jezler's work has been checked by a number of authors. Most of those who used the test on a large number of cases have corroborated his results, i.e. that strong reactions were obtained in cirrhosis (Table I) and that positive reactions in other diseases were uncommon.

Van Ginkel (7) omitted the use of fuchsin which he did not consider necessary to the reaction, employed dilutions up to 1:128 only. Crane (8) likewise omitted fuchsin and used 1:64 as his highest dilution. Hafström (9) and Schindel and Barth (10), both of whom

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added basic fuchsin to the reagent solution in their earlier investigations, later agreed that the fuchsin served no purpose.

Rohrer (11) did 125 tests on 108 patients: Among these were 18 positive reactions, 15 of which were in cases of Laennec's cirrhosis; the others included 2

TABLE I
*Results of the Takata reaction in Laennec's cirrhosis
of the liver by various authors*

plain test tubes, allowed to clot, later centrifuged. 1 cc. of serum was removed. 1 cc. of 0.9% NaCl was added to each of 8 Wassermann tubes 1.1 cm. in diameter and 12.5 cm. in length. The serum was pipetted into the first of these and serial geometric dilutions were made from 1:2 to 1:256. The fluid was pipetted

of the type of color change. In general (1) designated a flocculent covering the bottom of the tube, (2) one which attained a height of 1 to 3 mm. and (3) one which was over 3 mm. in height. Thus, a strongly positive result would read 00233210, a more weakly positive 00011100. With very few exceptions there

TABLE II
Results of mercuric chloride test in various diseases

Diagnosis	Author	Rohrer	Jexler	Van Ginkel	Crane	Schindell and Barth	Rappolt	Manche and Margonis	Wayburn and Cherry	Total Number of Cases	Total Number of Positive Reactions	Percentage of Positive Reactions
Laennec's Cirrhosis	No. Cases	15	176	21	25	13	75	66	94	483	398	82.4%
	No. +	14	124	16	20	12	61	64	87			
Tumor Metastases in Liver	No. Cases	18	28	7	6	9	?	14	37	119	20	16.8%
	No. +	4	3	5	0	7	?	0	1			
Chronic Passive Congestion	No. Cases	27	218	4	?	17	?	35	122	453	60	13.2%
	No. +	5	28	3	?	13	?	2	9			
Toxic Hepatitis (Calarrhni Jaundice)	No. Cases	5	39	2	7	15	17	29	24	138	15	10.8%
	No. +	1	7	0	0	1	3	1	2			
Cholelithiasis Cholecystitis	No. Cases	2	69	2	7	32	14	46	20	182	10	5.5%
	No. +	0	3	0	0	4	1	2	0			
Chronic Alcoholism	No. Cases	13	32	2	?	?	50	?	90	187	5	2.6%
	No. +	3	3	0	?	?	0	?	0			
Tuberculosis	No. Cases	7	68	8	16	11	?	50	58	212	19	8.9%
	No. +	0	7	2	0	3	?	4	3			

back and forth 4 to 5 times for each dilution; the final cc. was thrown away. To each tube was added 0.25 cc. of 10% anhydrous Na_2CO_3 , followed by 0.15 cc. of 0.5% HgCl_2 . The entire rack was agitated thoroughly 30 to 40 seconds after the addition of Na_2CO_3 ; the individual tubes were shaken as soon as HgCl_2 was added to each. In a number of duplicate tests done throughout the early stages of the experiment basic fuchsin was mixed with the HgCl_2 and 0.5 c.c. of the resulting reagent was used in place of the HgCl_2 alone, but was found to result in a lesser number of clear-cut positive reactions and more equivocal ones. The tubes were left at room temperature for 24 hours before reading. In a number of cases readings were also made immediately, after several or after 48 hours but none were found to be as good as the 24 hour reading.

A characteristic precipitate occurred in tubes from sera which were considered positive. This was a white to pearl-gray, soft, large-flaked flocculent. In order that a given sera be considered positive it was necessary for this type of precipitate to occur in at least 3 consecutive tubes. In actuality this began in the dilutions of 1:8 to 1:16. The appearance of a fine granular, usually brick red precipitate was common in the highest dilutions and of no significance. Indeed the use of only 6 tubes as advocated by Crane is rational, although we believe that the results can be shown more clearly with 8. The readings were recorded after the form of the Lange colloidal gold test, the amount of precipitate present being used as the index instead

was no difficulty at all in the readings; this became more apparent as our familiarity with the technique increased. Fig. 1 shows a result of the strongly positive type (from patient B—who had cirrhosis of the liver); Fig. 2 shows the same test after being shaken. (00023332)

RESULTS

The detailed results of the Takata reaction in all types of disease are shown in Table III. The majority of the diagnoses are clinical, but particular effort was made to check up the results of the test in the autopsy material.* There was a total of 94 cases of portal cirrhosis of the liver, 79 of these being considered in the advanced and 15 in the early stages of the disease. The criteria of advanced cirrhosis were emaciation, ascites, marked anemia, hemorrhage, variable icterus, spider hemangiomas, collateral circulation, changes in the carbohydrate metabolism, a hard liver, either large or small, known presence of the disease for some time, incapability of clinical improvement, rapid progress to exitus. The cases designated as early were in better physical condition, had hard livers, usually moderately enlarged, slight or no anemia, slight or no evidence of bleeding, no X-ray evidence of esophageal varices, few or no spider hemangiomas, little urobilin in the urine, and usually improved under treatment in the hospital. Among the advanced cirrhotics there

*We express our appreciation to Dr. Alvin Cox of the Stanford University Department of Pathology for his assistance in judging the pathological material and to Miss Anna Hall for valuable technical assistance.

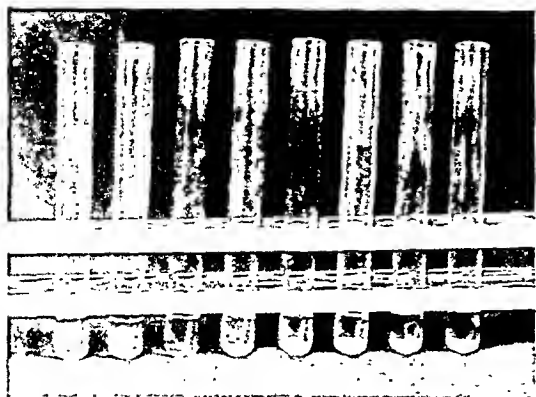


Fig. 1

were 73 positive and 6 negative reactions, a total of 92.4% of positive reactions. Among 35 advanced cirrhoses proven by autopsy there was a positive reaction in 100%. Of 2 early cirrhoses checked by necropsy, on the other hand, 1 gave a negative reaction. The cases diagnosed clinically only as early cirrhosis, however, were all positive, making a total of 14 out of 15 positive reactions or 93.3% which is a figure essentially the same as that obtained in the more advanced cases. There were, very possibly some cases in which some pathological evidence of cirrhosis may have been present in which no clinical diagnosis of cirrhosis was made and the Takata reaction still negative, but it is noteworthy that among 142 autopsies on tested patients there was only 1.

There were 5 cases in which the diagnosis of acute yellow atrophy was made: 4 of these died, all coming to autopsy; 1 recovered. This latter case clinically and 1 other, in which pathological proof was found, had also underlying cirrhosis. Both of these had strongly positive Takata reactions. Another case with a positive reaction (00033320) showed pathologically extensive toxic necrosis of the liver. The other 2 showed no pathological evidence of cirrhosis and both had repeated completely negative Takata reactions (00000000).

There were a number of conditions in which there

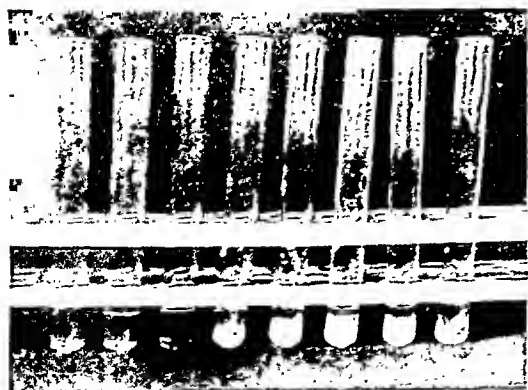


Fig. 2

was intrinsic involvement of the liver without the presence of portal cirrhosis; in almost all of these cases the diagnosis was confirmed by or made by autopsy: 1 case of portal thrombosis with multiple liver abscesses gave 00331100 while 3 cases of liver abscesses without portal thrombosis were all negative (00000000). 3 cases of Banti's syndrome and 2 of splenic and portal thrombosis gave consistently negative results. There were 3 cases with extensive cholangitis followed by irregular increase of the peri-portal connective tissue. In none of these was there a positive Takata reaction. There were 4 cases, 3 pathologically proven, of tuberculosis of the liver without cirrhotic changes, 3 of which gave negative Takata reactions and 1 a positive (00012200). 1 case with both tuberculosis and cirrhosis had a positive Takata reaction (00111000).

In the group designated acute hepatitis are included the cases of simple catarrhal jaundice, cases with jaundice following the administration of heavy metals, notably arsphenamine, and a few apparently more severe cases of jaundice indistinguishable in onset from catarrhal jaundice but more severe in their course. Among 24 cases in this group there were 2 positive reactions, both having the weakest type of positive, 00011100.

There were 20 cases of cholecystitis and cholelithiasis, all of which were uniformly negative (00000000). 1 case of gumma of the liver and 2 cases of hemolytic jaundice were likewise negative.

There were 37 cases of primary and secondary carcinomatous invasion of the liver: 4 of these were primary in the stomach, 10 in the pancreas, 3 in the gall bladder, 1 in the intrahepatic bile ducts, 1 in the ampulla of Vater and 18 elsewhere. All gave uniformly negative reactions with 1 exception. This case, clinically diagnosed as carcinoma of the breast, showed a Takata reaction of 02333000. At autopsy there was found widespread growth of carcinoma associated with proliferation of dense fibrous tissue in the region of the portal spaces.

Among the diseases with chief involvement outside the biliary tract cardiac decompensation from various causes with accompanying passive congestion of the liver ranks first. There were 122 cases in this group with 9 positive reactions or 7.4%. In practically all of these the decompensation was of considerable degree and duration. In 1 case in which there was improvement of the decompensation the Takata reaction became negative with the change in the clinical condition.

Pneumonia is mentioned with particular interest inasmuch as the test was first used to differentiate between the lobar and lobular types of pneumonia. In this series there were 31 lobular pneumonias with no positive reactions and 24 lobar pneumonias with 2 positive reactions (00233100) during the acute febrile stage of the disease. 1 of these patients died of pneumonia without autopsy. The other, two months later, was entirely negative and then again became positive (00012220). This patient had long standing Graves' disease.

There were 58 cases of pulmonary tuberculosis without cirrhosis of the liver. Of these 3 were positive, 2 having had thoracoplasty and a chronic course and 1 a history of cholecystitis.

Occasional positive reactions were found in miscellaneous diseases. These were mostly of the weak

variety: They included 1 out of 7 cases of subacute bacterial endocarditis and 1 out of 5 of lung abscess. There were 3 cases of acute glomerular nephritis and 1 acute flare up of chronic glomerular nephritis, all of which gave positive reactions. All of 24 other cases of chronic glomerular nephritis gave negative reactions.

Finally, there were 5 other instances in which a transient positive reaction appeared: A case of leprosy with artificially induced hyperpyrexia; 1 out of 21 cases of diabetes—this reaction occurred while the patient was in coma, disappeared with his emergence (although diabetes was still present); 1 case of ulcerative colitis; 1 out of 4 cases of exfoliative dermatitis, (a follow-up two years later showed this man without dermatitis, with a firm, slightly large liver and a Takata reaction of 00000000); and 1 case of inguinal hernia during strangulation. The remainder of the cases were entirely negative in their reaction. These include the following:

Chronic alcoholism 90 (including 18 fatty alcoholic livers, 51 chronic alcoholism, 21 pellagra and peripheral neuritis), arteriosclerosis 9, hypertensive vascular disease 7, coronary thrombosis 23, bronchial asthma 3, pneumoconiosis 2, upper respiratory infection 11, pleurisy with effusion 11, empyema 6, pharyngitis 2, tonsillitis 3, sinusitis 3, Graves' disease 12, peptic ulcer 50, duodenal diverticulum 4, acute appendicitis 7, pancreatitis 3, tuberculous peritonitis 2, miscellaneous carcinomata without liver metastases 28, normal pregnancy 2, toxemia of pregnancy 43, incomplete abortion 4, pyelitis 5, hypertrophied prostate 2, pelvic inflammatory disease 13, gonorrheal urethritis 4, urethral stricture 2, central nervous system syphilis 13, psychoneurosis 6, cerebral thrombosis 12, meningitis 5, osteomyelitis 2, fractured ribs 3, fractured jaw 2, sacro-iliac slip 3, head injury 3, arthritis 10, pernicious anemia 6, myelogenous leukemia 7, lymphoblastoma 6, anemia (not classified) 4, gangrene

TABLE III
The Takata reaction
Results of mercuric chloride test in 1025 cases

Diagnosis	All Cases (Clinical and Autopsy Diagnoses)			Cases Proven by Autopsy		
	Number	Positive	Negative	Number	Positive	Negative
Laennec's Cirrhosis (advanced)	77	71 (92.2%)	6	33 (12)	33	0
Laennec's Cirrhosis (early)	15	14 (93.3%)	1	2	1	1
Laennec's Cirrhosis (plus yellow atrophy)	2	2 (100%)	0	2	2	0
Acute Yellow Atrophy	3	1 (33.3%)	2	3	1	2
Cholangitic Cirrhosis	3	0	3	3	0	3
Liver Abscess	3	0	3	3 (2†)	0	3
Portal Thrombosis	3	1	2	3	1	2
Banti's Syndrome	3	0	3	1	0	1
Acute Hepatitis (and catarrhal jaundice)	24	2 (8.3%)	22	0	0	0
Carcinoma Metastases in Liver	37	1 (2.7%)	36	27	1	26
Tuberculosis of the Liver	4	1	3	3	0	3
Gumma of the Liver	1	0	1	0	0	0
Familial Hemolytic Jaundice	2	0	2	1	0	1
Chronic Passive Congestion	122	9 (7.4%)	113	20	2	18
Cholecystitis and Cholelithiasis	20	0	20	2	0	2
Acute Nephritis	4	4 (100%)	0	2	2	0
Chronic Nephritis	24	0	24	3	0	3
Lobar Pneumonia	24	2 (8.3%)	22	2	0	2
Lobular Pneumonia	31	0	31	9	0	9
Pulmonary Tuberculosis	58	3 (5.2%)	55	6	1	5
Subacute Bacterial Endocarditis	7	1	6	2	0	2
Lung Abscess	5	1	4	1	0	1
Diabetes*	21	1	20	0	0	0
Exfoliative Dermatitis*	4	1	3	0	0	0
Ulcerative Colitis*	1	1	0	0	0	0
Leprosy*	1	1	0	0	0	0
Strangulated Hernia*	1	1	0	0	0	0
Miscellaneous (see text)	525	0	525	15	0	15
Total Cases	1025	118	907	143 (32)	44	99

*Transient positives.

†Proven by biopsy.

2, sciatica 2, abscess and cellulitis 19, undiagnosed disease 11, normals 7, and of the following 1 each:

Epilepsy, beri-beri, hydrocele, erysipelas, botulism, epithelioma, bichloride poisoning, gastritis, Addison's disease, pericarditis, fractured arm, migraine, bromide poisoning, morphine addiction, neurocirculatory asthenia, tenosynovitis, metrorrhagia, bladder stones, kidney stone, chancre, epididymitis, rectovesical fistula, gastro-ecolic fistula, arsenic poisoning, Parkinson's disease, Ayerza's disease, bowel obstruction, salmonella infection, amyloid kidney, purpura, cystic lung, cocaine poisoning, agranulocytosis, Paget's disease, brain tumor, duodenal anomaly, Vincent's angina, amputation neuroma, bronchial stenosis, fractured patella, tuberculosis of the kidney, mucous colitis, malaria, spontaneous pneumothorax, gastro-enteritis, acute enteritis, chronic lymphatic leukemia, pyelonephrosis, infectious mononucleosis, malnutrition, lipid nephrosis.

In the entire series of 1025 cases a positive Takata reaction occurred 118 times. In 87 cases the disease involved was cirrhosis of the liver; in another 6 cases there was severe liver damage; if circulatory changes in the liver may be added to this list another 9 cases are included; 3 more cases had acute glomerular nephritis and 1 had an acute flare up of chronic nephritis; this leaves only 12 positive reactions (5 of which were transient) in 717 cases or a percentage of what might be termed false positives of 1.7. If all cases other than Laennec's cirrhosis are separated there are 31 out of 931 cases or 3.3%.

COMMENT

The results obtained with the mercuric chloride test in this series have been decisively clear cut. As our familiarity with it increased the boundary line between positive and negative became sharper, the percentage smaller of what might be termed "false positives." We were able to do away entirely with the equivocal types of reading advocated by some authors i.e. reading of 1 or 2 tubes as a positive, reading at various time intervals, reading granular precipitates, interpreting color changes. We feel that this makes the test more practically useful.

The statistics on cirrhosis agree in essential parts with those of Jezler, Rohrer, Skouge, Lazzaro, Crane, Schindel and Barth, Ragins, Rappolt, Maneke and Margonis. Hafstrom obtained positives in all 17 of the cases of Laennec's cirrhosis which he described but also found positive tests in numerous other diseases including those from which cirrhosis may be identified by the test. However, Hafstrom counted as positive flocculents—judging from the photographs in his article—various types of precipitation, including the granular type which we regard as irrelevant. He also considers precipitation in 1 tube as a positive reaction. Heath recorded positive tests when precipitation was maximum in 1 or very slight in 3 to 5 tubes, dividing his readings into 5 separate classes. He has, moreover, a large number of cases with "cirrhosis probably present" in whom a negative Takata reaction was found, but in which the correct diagnosis was also questionable; among cases with "established cirrhosis" 28 out of 35 results were positive (80% positive as opposed to 60% in his entire series). Heath's example was followed by Magath whose percentage of positives is likewise small. In our experience the Takata test is more liable to be correct

than the clinician and we feel with Jezler that the clinical diagnosis of cirrhosis is too frequently made.

Although we hesitate in disagreement with Jezler (1934) to proclaim the Takata reaction as a specific test for portal cirrhosis of the liver, our pathological even more than our clinical statistics indicate that a positive reaction in other liver diseases as well as in the population at large is such a rarity that from a practical standpoint it may be regarded as a specific test. In this respect it may be compared to the Wassermann test in syphilis or to the elevation of the blood urea in chronic glomerular nephritis. Neither are specific for their respective diseases and either may occur in other conditions but the presence of either is regarded as information of considerable importance. Thus, while only 1 out of 37 cases of early and advanced cirrhosis proven by autopsy (including 2 cases of yellow atrophy plus cirrhosis) was negative, only 3 out of 43 autopsied cases of other diseases of the liver were positive. One of these was portal thrombosis with multiple liver abscesses, the second clinically acute yellow atrophy and pathologically toxic necrosis of the liver, the third metastatic carcinoma. The amount of liver damage in these 43 cases as well as in 63 other cases not regarded as primarily involving the liver was often extremely marked (of 105 livers, "advanced" in 18, "moderate" in 40). In 7 of the carcinomatous livers the tissue had been very largely replaced by cancer cells; in the 2 cases of acute yellow atrophy with a negative reaction there was extensive toxic necrosis with very little actual liver tissue remaining, this was also true in 2 cases of severe amyloidosis. On the other hand, among the 37 cases of cirrhosis there were 4 instances in which microscopically there was very slight evidence of disease except for the fibrosis (one of the least involved was the case with the negative reaction).

The consistent occurrence of a negative reaction in all of 3 cases of cholangitis with ensuing cirrhosis diagnosed both clinically and pathologically is very interesting. These had changes microscopically as marked as cases of Laennec's cirrhosis with positive reactions. One may raise the question of the similar etiology of late cirrhoses which react negatively.

The occurrence of flocculation in all of 3 cases of acute glomerular nephritis is worthy of comment. Jezler's article affirming the high incidence of the Takata reaction in this condition was unfortunately not read until this series was well under way. The only case of chronic nephritis which had an acute exacerbation after we became aware of the likelihood of a positive reaction during a flare-up did have a positive Takata test although it had been previously negative. The activity of the other 24 cases of chronic nephritis at the time blood was taken for the test cannot be judged.

Clinical Value: Regardless of the fact that the Takata reaction is positive in so great a percentage of cases of cirrhosis of the liver as to be regarded as almost though not entirely specific, one may question its use in the individual instance. There have been certain types of cases in which the Takata reaction has been specifically helpful in differential diagnosis and has given the correct answer when the clinical diagnosis was in doubt or was wrong. In considerable part the confirmation was in the autopsy or in the operating room. These include 7 cases with marked jaundice in which a differentiation was made from carcinoma,

of acute hepatitis; 9 there was a question of Bart's syndrome. In acute the diagnosis of was made on the basis of 12 cases the diagnosis of that of acute hepatitis before the Takata reaction. Four of 4 cases by a positive Takata reaction in 10 other cases which this disease could occurrence of a negative.

There were 7 cases of as developing cirrhosis in reaction were made over. These were patients in which originally negative and reaction was clinically slight amount of protein, increasingly great. One 215 35, M. M., a 34: noted for peripheral Nijmegen, ascites, or 1 m. Liver palpable. F. Takata reaction 0000000 621 35, readmitted 18 cm. below right c. Takata index 57. Takata 726 35, improving. I Abdomen smaller. Ict.

12 31 35, admitted f. anemia. Icteric index 4 2 3 36, improving. Ta 1 3 37, readmitted for ascites, hard liver 14. Icteric index 31, Takata

This patient clinically ing hepatitis with development paralleled the precipitation occurring in disease progressed. It reaction process was Takata reaction was positive we have, however, true—extensive liver fibrosis also. T Takata reaction was positive precipitation; 2 of reaction. If blood were when they were noted among the negative account for the

MECHANISM OF

Many theories have been advanced which mercuric chloride and flocculation of proteins which are in pathologic solution occurs in albumin-globulin reaction of the globulin. The method, for

stone or acute hepatitis; 9 cases with ascites in which there was a question of carcinomatous metastases or of Banti's syndrome. In 11 cases with or without ascites the diagnosis of cirrhosis instead of carcinoma was made on the basis of a positive Takata reaction. In 2 cases the diagnosis of cirrhosis was preferred to that of acute hepatitis because of a very strong positive Takata reaction. Early cirrhosis of the liver was found in 4 cases by checking back after the occurrence of a positive Takata reaction done as a routine test. In 10 other cases which were at first considered cirrhosis this disease could be ruled out because of the occurrence of a negative Takata reaction.

There were 7 cases of what we choose to designate as developing cirrhosis in which serial studies of the reaction were made over a period of months or years. These were patients in whom the Takata reaction was originally negative and in whom the evidence of cirrhosis was clinically slight. As the disease progressed the amount of precipitation which occurred became increasingly great. One example of this may be given:

2/15/35, M. M., a 34 year old married woman admitted for peripheral neuritis and chronic alcoholism. No jaundice, ascites, or evidence of collateral circulation. Liver palpable. Few small spider hemangiomas. Takata reaction 00000000.

6/21/35, readmitted for pellagra and acute hepatitis following prolonged period of drinking. Liver tender, 18 cm. below right costal margin. Ascites present. Icterus index 57. Takata reaction 00012000.

7/26/35, improving. Liver smaller and less tender. Abdomen smaller. Icterus index 22.9. Takata reaction 00002000.

12/31/35, admitted for hematemesis. Macrocytic anemia. Icteric index 41. Takata reaction 00023321.

2/8/36, improving. Takata reaction 00012300.

1/8/37, readmitted for hematemesis. Marked anemia, ascites, hard liver 14 cm. below right costal margin. Icteric index 31, Takata reaction 00033321.

This patient clinically was a case of severe recurring hepatitis with developing cirrhosis. The Takata reaction paralleled the clinical course of the disease, precipitation occurring in more and more tubes as the disease progressed. It may be argued that the cirrhotic process was already far advanced before the Takata reaction was positive. The autopsy material which we have, however, favors the view that this is not true—extensive liver degeneration may be present but not fibrosis also. There were 4 cirrhotics who had a positive Takata reaction who later showed marked improvement accompanied by a decreasing amount of precipitation; 2 of these developed a totally negative reaction. If blood were taken from such patients only when they were entirely quiescent they would be classed among the negative reactors—undoubtedly this does account for the majority of such in this series.

MECHANISM OF THE TAKATA REACTION

Many theories have been advanced to explain the flocculation which occurs. It is generally believed that mercuric chloride and sodium carbonate form a colloidal solution of mercuric oxide in the presence of proteins which are considered to act as protective colloids; in pathological states precipitation of the colloidal solution occurs: Takata himself thought that the albumin-globulin ratio became altered by increase of the globulin fraction (1925). Jezler (4) using the Kjeldahl method, found the globulin fraction con-

stantly over 55% of the total protein in cases with positive mercuric chloride reactions while it averaged around 37% in cases with negative reactions.

Lazzaro (14), Hugonot and Sohler (28), Carrière, Martin and Dufossé (29), Ragins (19), Vigada and Montanari (30), believed that the reaction was dependent on the lowering of the albumin-globulin ratio of the serum. Van Ginkel (7), Rappolt (20), Kirk (23), Gros (31), Hohn (32) and Ucko (33) consider the increase in the serum globulin as the important factor.

On the other hand Skouge (13) and Schindel and Barth (16) found no constancy in the correlation between the occurrence of a positive Takata reaction and either increase in the globulin fraction or lowering of the albumin-globulin ratio. Allesandro (34) working with phosphorus poisoned rabbits agreed with the latter views. Schreuder (35) believed that a positive reaction occurred with either increase of the globulin or decrease of the albumin content.

Medvei and Paschkis (36) found that the addition of heparin to Takata positive sera changed the reaction from positive to negative, although the addition of heparin had been shown by A. Fischer to convert serum albumin into serum globulin.

Schindel (37) added various lower fatty acids to sera with negative Takata reaction to produce flocculation, believed that ketonuria might play a role in the production of the reaction. Gros (31) found no change in the reaction before and after extraction of the fatty acids from the serum. Kallos-Deffner (38) obtained positive reactions in the sera of rabbits with ketonuria produced by starvation or existence in a rarified atmosphere; with restoration of normal conditions the Takata reaction became negative. Allesandro (34) found that a positive Takata reaction in his experimental rabbits was constantly accompanied by a ketonuria. Recht (39) found a positive Takata reaction in children with acidosis and dehydration. In our series were at least 2 cases in which such a mechanism is conceivable. One was a diabetic coma with marked ketosis; the Takata reaction was 00001221; 2 days later the patient was clinically improved, had no ketosis, a Takata reaction of 00000000; several checks showed that this remained negative. A similar result was true in a case of leprosy which had been given artificial hyperpyrexia; at the height of the fever the Takata reaction was 00002333; twice afterwards it was 00000000. (It may be noted that in both these cases precipitation begins in a dilution higher than it does in the cases of cirrhosis).

Oefelein (40) found the ammonia content of the blood high in cases with positive Takata reactions.

Staub and Jezler (41) conclude that the Takata reaction represents not a function but a dysfunction of the liver, dependent on the colloidal composition of the serum.

Jurgens (42) found the Takata reaction negative after removal of the liver in geese, positive after tying the portal vein; in dogs it was positive after the production of an Eck fistula, negative after reversed Eck fistula. He concludes that the test is dependent on the products of metabolism of the damaged liver cells.

Crane (8) suggests as possible causes for a positive Takata reaction:

1. Release of liver proteins into the circulation (i.e. in cases of yellow atrophy).

2. Inability of the liver to alter proteins contained in the blood.

3. Failure of some blood to pass through the liver, going instead (by way of collateral venous anastomoses) directly into the general circulation.

It is extremely difficult to explain the occurrence of the positive Takata reaction by any one hypothesis. Increase in the globulin fraction of the serum, both relatively and absolutely, does occur in the majority of the cases but there are many cases in which it does not. Conversely, there are many cases with changes in the globulin without positive Takata reaction. The presence of liver damage as such appears to play very little role. If the release of liver proteins into the circulation were important acute yellow atrophy should give uniformly strongly positive reactions, but does not. If the reaction were caused by the failure of blood to pass through the liver portal thrombosis should give uniformly positive reactions, but does not. It seems rational at this time to be content with Staub and Jezler that the Takata reaction represents a dysfunction of the liver. It probably is dependent on the colloidal composition of the serum. It probably represents some retention substance which under the usual conditions of its occurrence requires some time to be formed in sufficient quantity to result in a positive reaction (comparable, again, to an elevated blood urea in chronic glomerular nephritis). It is possible that this is a toxic product.

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SUMMARY

The mercuric chloride flocculation test of Takata was performed on 1025 cases. A positive reaction occurred 118 times or 11.5%. In 94 cases of cirrhosis of the liver there were 87 positive reactions, a percentage of 92.5.

The percentage of positives in all conditions was 3.3% (of 931 cases), a total of 31 cases. Included in this number were 6 out of 81 cases of severe liver involvement, or 7.4%, 10 out of 122 cases of cardiac decompensation or 7.4% and 4 out of 4 cases of acute nephritis.

CONCLUSIONS

1. The Takata reaction is an excellent test in the diagnosis of Laennec's cirrhosis of the liver.
2. It is of particular value in differentiating cirrhosis from carcinoma with metastases in the liver, in cases with jaundice or with ascites.
3. Liver damage, as such, in the absence of Laennec's cirrhosis, yields a low percentage of positive reactions.
4. Failure of precipitation in a questionable case is a fairly certain indication that cirrhosis is not present.
5. In a few instances the diagnosis of cirrhosis can be made before clinical signs appear.
6. In developing cirrhosis the reaction may be negative at first, to become positive as the disease progresses.

Chronic

FROM 1922 until the end of the Beth-El Hospital. Since 1922 the patients for this illness. The history of chronic n. ... write during the present ... the recent literature ... present an analysis of ... limited to our institution.

DEFL.

Chronic ulcerative colitis of the colon, ... involving the ... course from the ... entity, not unc ... and inter ... frequently

ETIO

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Because of the appearance in some patients ... deficiency in ... for the onset of ... appear to be borne ... in individuals ... to any marked ... cases showed ... patients present

From the Department of ... Beth-El Hospital, Brockton, ... the ... October 10, 1937.

Chronic Ulcerative Colitis: An Analysis of 88 Cases*

By

ISIDORE A. FEDER, M.D.
BROOKLYN, NEW YORK

FROM 1922 until the end of 1930 there were admitted to the Beth-El Hospital 23 cases of chronic ulcerative colitis. Since 1930 we have treated 65 patients for this illness. This marked increase in incidence of chronic ulcerative colitis on our hospital service during the present decade has prompted us to review the recent literature relative to this disease and to present an analysis of the 88 cases which have been admitted to our institution.

DEFINITION

Chronic ulcerative colitis is an inflammatory condition of the colon, usually extending upwards from the anus, involving the colon either partially or along its entire course from the anus to the cecum. It is a specific entity, not uncommon in incidence, running a prolonged and intermittent course, with serious complications and frequently fatal in its outcome.

ETIOLOGY

The signs and symptoms in the patient who presents himself for examination and treatment unquestionably point to the infectious nature of the disease. Much difference of opinion has existed relative to the etiology of this condition. Is infection the primary etiological factor? Is infection secondarily imposed upon a colon which, for other reasons, has lost its normal resistance to bacteria which ordinarily inhabit it? Is the infection similar or akin to other well known forms of colon inflammation? The confusion resulting from the answers to these questions has complicated the approach to the disease and made more difficult the method of treating it.

Evans (1) suggests that the terms pylorospasm, gastritis or duodenitis, and peptic ulcer represent steps of one disease process in the stomach or duodenum and that the disease is manifest in the colon through spastic colitis, mucous colitis, catarrhal and ulcerative colitis. Drucek (2), Kuttner (3), and many other recent writers hold that ulcerative colitis indicates a late stage of the spastic colon. On the other hand Barger (4) states that the number of cases in which chronic ulcerative colitis follows the irritable colon is very small, and would not justify the belief that the latter is a forerunner of chronic ulcerative colitis.

Because of the appearance of symptoms of avitaminosis in some patients certain authors have felt that vitamin deficiency in some form may be the initial cause for the onset of the disease. This concept does not appear to be borne out clinically. All of our cases occurred in individuals whose dietetic habits did not deviate to any marked degree from the normal. Three of our cases showed evidence of vitamin deficiency. Two patients presented the skin manifestations of

pellagra and in one the beriberi type of heart was discovered at autopsy. In view of the fact that these symptoms appeared either in the late or terminal stages of the disease, it is assumed that the vitamin deficiency is rather a result of improper absorption and utilization in, than a cause of, chronic ulcerative colitis. Dukes (5) and Barger (4), who have carried out studies of the life habits of many series of patients found no evidence of vitamin or other deficiency playing a part in the causation of the disease.

Some authors have ascribed a disturbed metabolism as an etiological factor. Portis (6) suggests a thyrotoxic cause for the disease. Basal metabolic readings in six of our patients showed the rates to be normal in four, slightly above normal in one and slightly below normal in another.

Recently the psychogenic origin of the disease has received considerable attention. Sullivan (7, 8) found psychological difficulties in 18 of 25 consecutive cases of ulcerative colitis, in 15 of which the emotional disturbances appeared to be of definite etiological significance. He found a well marked time relationship between emotional crises and the onset of the disease or its recurrences. Murray's (9, 10) reports are confirmatory of this idea. Reehad (30) and Sullivan (8) found that psychotherapy was a successful method of treatment in chronic ulcerative colitis. 72% of our cases occurred in young adults between the ages of 16 and 40, in many of whom the problems of sex, marriage or finances might have been responsible for the creation of a psychological conflict. Five of our patients gave histories of having had "nervous breakdowns" previous to the onset of the colitis. We have called attention to the marked increase in the number of cases at our hospital since 1930. It is of interest to note that this is coincident with the period of economic depression which set in at that time. Economic and financial worries may possibly have been the exciting factors in a number of these patients.

Turner (11), Hurst (5), Hern (12) and Penner (13) feel that the disease is a form of bacillary dysentery. Winkelstein (14) reports that 20% of his cases are due to this condition. These authors base their reasoning on the response of many patients to specific treatment with anti-dysenteric serum. However, as Dukes (5) and Barger (4) point out, the negative bacteriological and epidemiological evidence, the absence of agglutination and the uncertain effect of antidyenteric serum seem to discount this point of view.

Fradkin (15), Winkelstein (14) and others feel that the ameba may be a cause of chronic ulcerative colitis. It is undoubtedly true that a number of cases of amebic colitis are mistakenly diagnosed as chronic ulcerative colitis. But where the diagnosis is not supported by laboratory evidence or by effects of anti-

*From the Department of Gastro-enterology, Service of Dr. Finkelstein, Beth-El Hospital, Brooklyn.
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Fig. 1

amebic therapy, one can hardly see any reason for attributing to this organism the responsibility for this disease.

Bassler (16) found that in young subjects *Clostridium Welchii*, enterococcus and green and non hemolytic streptococcus is the infective trilogy and that in adults the hemolytic streptococcus is most often met with.

Bargen (4) and other workers have established a diplostreptococcus of characteristic morphologic and biologic properties as the main causative organism of chronic ulcerative colitis. The diplococci, when isolated according to the method of Bargen, are fused in pairs, almost merging into chains of four cocci, are lancet shaped and gram positive. The diplococcus has been isolated in pure culture from the rectal lesions of 80% of his cases at the Mayo Clinic. The lesions of ulcerative colitis have been reproduced in rabbits and dogs by the intravenous injections of many strains of this organism. It has been recovered from the blood in acute fulminating cases. It has been found in foci of infection such as peridental or peritonsillar abscesses and cultures of these reproduced the disease in animals. Cock (17) produced periapical dental infections in dogs and two to 16 months later the proctoscopic picture of chronic ulcerative colitis was demonstrated. People in normal health have been found to be carriers of this organism. It has been isolated in the stools of patients with vague abdominal complaints who later developed the typical picture of chronic ulcerative colitis.

Many authors have cast doubt upon the contention of Bargen that the diplostreptococcus is the chief offending organism. Portis (6) states that no positive blood cultures are found. However, one can rarely obtain positive blood cultures in most diseases which have been initiated by infection from a distant focus. Bassler (17) recovered the diplococcus in 44% of his cases of ulcerative colitis and in 37% of 500 cases of

non-ulcerative colitis, yet feels that it is not the etiological factor in the disease. Rafsky (18) states that the diplococcus is a strain of the enterococci group. Bargen has definitely shown significant differences between the two; namely that on mannite agar the appearance of the colony of the diplococcus is fine and translucent; the enterococcus grows as a large, white opalescent colony on this medium. The diplococcus does not grow on plain agar; it does not grow on gelatin; it usually does not coagulate milk. The enterococcus does all of these readily. Dukes (5) feels that the diplococcus and other types of fecal streptococci are secondary invaders and that the bloody diarrhea produced by intravenous injection in rabbits does not follow the course of human chronic ulcerative colitis and that the same result is produced by other bacteria.

In our series of cases the diplostreptococcus was isolated from 16 patients or 18% of the total. Rarely did we make repeated examinations after failure to isolate the organism on the first attempt. It is probable that, if the technical details and suggestions of Bargen were carefully followed out, many more cases would reveal the diplococcus as the offending organism. The enterococcus was isolated in six cases or 7% of the total. A green streptococcus was isolated in two patients and a hemolytic staphylococcus in one. No specific organism was isolated in 63 patients or 72% of the entire group.

The exacerbations of this disease following upper respiratory infections and the removal of foci of infection lend support to the belief that the disease is infectious in nature. Seven of our patients had acute exacerbations after upper respiratory infections and one after a pleurisy. Tonsillectomy caused an exacerbation in one. The extraction of a number of teeth led to an acute fulminating exacerbation in one case with death from sepsis.

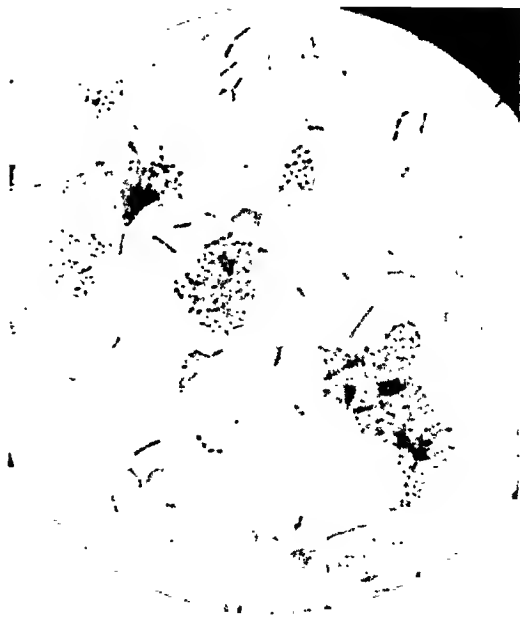


Fig. 2

The following report substantiates in every detail Bergen's claims as to the etiology of chronic ulcerative colitis and clearly illustrates the role of a focus of infection in the onset and recurrence of symptoms.

Case No. 57081, J. S., male, age 17. Admitted January 9, 1933, with a history that two months prior to admission, following a cold, the patient developed a diarrhea and shortly thereafter noticed blood in the stools. After treatment with medicines his condition improved. He then had another upper respiratory infection which brought with it a more severe recurrence of symptoms and hospitalization was advised. On admission, patient was having numerous loose stools containing blood and pus and on many occasions passed only clots of blood. There were severe abdominal cramps and marked weakness. Temperature was 103. White blood cells numbered 20,200 with 80% polymorphonuclear cells. Hemoglobin was 55% and red cell count 2,575,000. Barium enema showed a spastic

admission tonsillectomy was performed. This was followed the next day by an increase in the number of stools which contained blood. Examination of the stool at this time showed numerous diplococci. Culture of the tonsils disclosed a pure culture of diplostreptococci, the same organisms which were noted in the stool. Another autogenous vaccine was prepared and administered for six weeks. Patient was discharged as cured on January 3, 1934. There has been no recurrence of symptoms to date.

Five patients had acute recurrences during pregnancy and two had therapeutic abortions performed for this reason. Two patients had recurrences after appendectomy and three after hemorrhoidectomy.

Patients of all ages and of both sexes are affected by this disease. The youngest in our series was seven years of age, the oldest 70. 62% of our cases occurred in females (Table 1).

In only one instance were two members of one

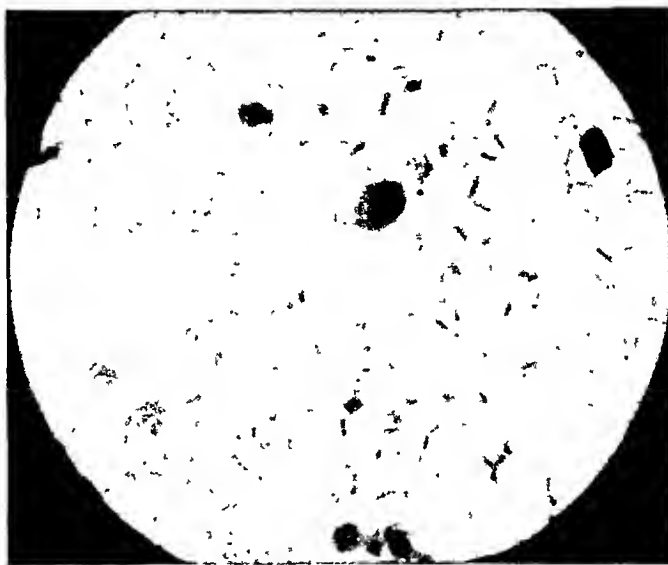


Fig. 3

colon which filled very rapidly. Sigmoidoscopy disclosed numerous ulcerations in the rectum and sigmoid, exuding a bloody and mucopurulent discharge. Smears taken from the stool and stained revealed a preponderance of diplococci singly and in chains (Fig. 1). Culture of the stool showed almost pure culture of the same organism. Repeated transfusions were given to tide the patient over the acute phase of his illness. A vaccine prepared from the organisms isolated in the stools was administered. Five weeks after administration of the vaccine direct smears from the stool showed clumps of agglutinated diplostreptococci (Fig. 2). (This was probably caused by the presence of agglutinins in the serum of the blood which had exuded through the colonic mucosa and agglutinated the organisms). The patient was discharged markedly improved on February 16, 1933. Vaccine treatment was continued at home for three months. At the end of this time no diplococci were found in either the smear (Fig. 3) or culture from the stool. Patient felt well and had three to four bowel movements per day which were occasionally streaked with blood. On November 4, 1933, patient was again ill with an upper respiratory infection. Shortly thereafter there was a recurrence of the severe diarrhea. He was readmitted to the hospital November 18, 1933, for tonsillectomy. Stool examination at this time failed to show the diplococcus. The number of stools lessened under medical treatment and a few weeks after

family affected; a young girl who developed symptoms shortly after the death of her sister from chronic ulcerative colitis.

SIGMOIDOSCOPY (GROSS PATHOLOGY)

In the greatest number of cases the pathologic process is initiated within the lower limits of the rectum and extends upward toward the sigmoid and descending colon. The initial stage is characterized by an acute inflammation of the mucous membrane of the colon. It appears diffusely hyperemic. This is shortly followed by an edema of the mucosa which becomes boggy and readily bleeds when slightly traumatized by the sigmoidoscope. Minute abscesses appear beneath the surface of the mucosa which slough away and leave small, pin point, bleeding ulcers. At this stage the mucous membrane appears diffusely granular and bleeding. The union of these minute ulcers may produce ulcers of larger dimensions and secondarily imposed infection will alter their appearance. During the stage of remission the pin point ulcers may heal and leave small scars. In the late stages of chronic ulcerative colitis, when great difficulty may be encountered in differentiating this disease from other forms of

colitis with ulcerations, the presence of these small, pit-like scars is of utmost importance in making the diagnosis. As a result of the diffuse scarification with formation of fibrous tissue the wall of the bowel becomes contracted and the lumen narrowed from slight to extreme degrees. Strictures may develop in cases where the pathologic process has been more severe and fibrosis more marked. Purulent exudate, dammed up by these strictures, may produce large abscesses.

seen. Only ragged strips and bridges of mucosa course irregularly across the inner aspect. Between these lie exposed submucosa, muscularis or serosa.

MICROSCOPIC EXAMINATION

The mucosa is for the most part absent. In one place most of the thickness of the submucosa is also gone. The cells along the surface of the mucosa show degeneration. In the mucosa there is an infiltration

TABLE I
Age incidence

Age	7	11-15	16-20	21-30	31-40	41-50	51-60	61-70	Total
Male	1	1	1	14	9	4	1	2	33
Female	0	3	12	21	6	6	5	2	55

When the ulcers heal, ragged polypoidal tags of mucous membrane remain. (These must not be confused with true adenomatous proliferations). When these infected ulcers extend into the deeper layers of the colon the danger of perforation is imminent.

The following chronologic reports exemplify the sequence of protoscopic findings in one of our cases:

Case No. 82697, F. L., female, age 16. Admitted March 4, 1937, with history of diarrhea of five weeks duration, the stools during the latter two weeks admixed with blood and pus. Sigmoidoscopy March 11th; markedly congested mucosa. Bleeds readily. Many small, whitish areas under the mucous membrane (Abscesses). Many small ulcerations. May 26th: Acutely congested mucosa. Many small and larger ulcerations. Many small, pit-like scars noted throughout the mucosa. July 7th: Mucosa much paler but thickened and scarred. Few polyps noted.

The following case exemplifies the ascending nature of chronic ulcerative colitis and the danger of pronouncing a patient cured without thorough and long follow up:

Case No. 32941, E. K., female, age 20. Admitted March 9, 1929, with a history of three days of bloody diarrhea. March 11th—proctoscopy reveals an ulcerative proctitis extending only two inches above the anus. Patient was apparently cured with rectal instillations of bismuth subnitrate in olive oil and discharged April 29th. Patient was readmitted on November 18, 1929. There was a recurrence of bloody diarrhea after an upper respiratory infection. Sigmoidoscopy revealed pin point abscesses with small and button sized ulcers throughout sigmoid and rectum, penetrating through the mucosa and submucosa.

The following gross and microscopic pathologic description indicates the marked destructive process in a case of longer standing:

Case No. 81796, M. J., female, age 29. Admitted January 13, 1937, with a history of diarrhea of four years duration. Patient died February 1, 1937, of a generalized peritonitis due to perforation of the colon. At about the hepatic flexure, small mucosal ulcerations are first noted. These grow very extensive along the transverse colon partly encircling the bowel. They possess ragged, undermined edges with a base made up of submucosa, muscularis, and along the attachment of the lesser omentum only peritoneum. The peritoneum presents longitudinal rents encircling the bowel, affording communication between the colon and peritoneal cavity. The descending colon, sigmoid and rectum present a more advanced degree of the lesions. The bowel is thickened to about 0.5 cm. No normal mucosa is

of lymphocytes and plasma cells and some edema. A few polymorphonuclear cells are also noted. Where the mucosa is absent the surface is covered with cellular debris and polymorphonuclear cells. There is an increase in fibrous tissue and some edema of the submucosa. It is infiltrated with lymphocytes, plasma cells, histiocytes and polymorphonuclear cells. A lymph node in the serosa shows a widening of its sinuses and these hold histiocytes.

SYMPTOMS AND DIAGNOSIS

The disease may start insidiously. The patient may complain of vague abdominal pains, increased frequency of stools with an excessive amount of mucous. The stools are loose in consistency. After a variable period of time the patient will notice blood admixed with the stool and later the presence of pus. There may be slight or even no elevation of temperature. The patient has frequent calls to stool and may pass only hemorrhagic or purulent rectal discharge without fecal matter. In the fulminating case there is a rather abrupt onset with high and occasionally septic type of temperature. The patient appears acutely ill. There are numerous loose purulent and bloody stools. The patient shows all evidence of a profound toxemia.

Later the patient presents a picture of inanition and dehydration. There is marked loss of weight, pallor and anxiety. 46% of our cases had a marked secondary anemia. 8% had achylia gastrica. The leucocyte count and sedimentation rate were increased especially in cases with hyperpyrexia.

The diagnosis rests upon the history and sigmoidoscopic findings as aforementioned, the physical examination and the appearance of the colon on the X-ray film after examination with the barium enema.

Physical examination of the abdomen will disclose a firm, tube-like descending colon and sigmoid which may be tender to palpation. Digital examination of the rectum discloses a spastic sphincter. The lumen is narrowed. The mucosa is granular and, if ulcerations are deep, they may be noted by the examining finger.

The appearance of the colon with the barium enema depends upon the stage of the disease, the extent of the ulceration and the presence of sequellae. The colon fills rapidly. Where the ulcerations are small and superficial the outline of the colon is smooth and shows a notable lack of haustration. Where the ulcerations are deeper the outlines of the colon are feathery, a

characteristic picture of the disease. Where ulceration is deep, and irregular fibrosis has occurred, the outline is rough and irregular. Because of the fibrosis of its wall the colon becomes narrowed and shortened. Examination by the contrast enema, where air is injected into the colon following the expulsion of the barium, will more easily outline ulcers and polyps.

COMPLICATIONS

Stricture of the bowel is commonly seen. It is the result of the fibrosis which takes place during the stage of healing. One is struck by this condition when one finds marked difficulty in passing the sigmoidoscope because of the narrowed lumen. It is wiser to stop the examination than to attempt to forcibly push one's way past the stricture. Perforation of the bowel resulted from this procedure in one of our early cases. 13 of our cases were complicated by stricture.

Polyposis (improperly termed because the polypoidal tags of mucous membrane which remain after healing are not true polyps) is frequently noticed on proctoscopic examination. If present higher up in the colon they are well visualized on the X-ray by means of the contrast enema. 11 of our cases were complicated by polyposis. When large these false polyps may aggravate the symptomatology.

Perforation of the colon with a resulting peritonitis occurs when ulceration has penetrated the serosa of the colon. This was observed in three and the cause of death in two of our cases. Penetration of ulcers in the perirectal and perianal regions may form perirectal abscesses which then may rupture through the skin, vagina or bladder and produce fistulae. Nine of our cases showed these complications.

Vitamin B deficiency was found in a case which revealed a beriberi type of heart at autopsy. There was myocardial atrophy, edema and vacuolation of the heart muscle. Two cases of vitamin G deficiency were noted—a roughness and dark discoloration of the backs of the hands and forearms as is seen in pellagra.

There was an inversion of the serum albumin and globulin ratio in two cases. There was hypoproteinemia in three cases, two of which revealed evidence of a nutritional edema.

Arthritis complicated two of our cases. Hepato and splenomegaly was found in one case.

Bargen (4) and Hurst (19) in addition note such complications as renal insufficiency, ocular lesions, peripheral neuritis, progressive arterial occlusion, multiple abscess of the liver, tetany and carcinoma. Carcinoma is not as common a complication as is found in true polyposis or multiple adenomata of the intestine. This is probably due to the fact that the polypoidal masses are not true adenomatous proliferations.

PROGNOSIS

Primary recovery within a few weeks has been reported. We have never seen it. Exacerbations and remissions are common. One must not fall into the error of pronouncing a case cured merely on freedom of symptoms or even with apparently healed lesions on examination of the colon, unless the patient has been followed up for a reasonably long period of time.

Hurst (19) feels the mortality should not exceed 5 to 10% if the patients receive adequate treatment for sufficient periods. He states that the large majority should recover eventually so completely that they are able to lead a life of normal activity. Bargen (20)

states that X-rays show a tendency of the bowel to return to normal in 40% of the cases. Crohn and Rosenak (21) in a series of 75 cases report 33 cured, 23 improved, 8 unimproved and 11 died. Kiefer (22) divides his cases into the non toxic—non sclerotic of which he reports 78% cured, the non toxic—sclerotic of which 50% recovered and the toxic where 38% showed satisfactory improvement and where the mortality was 25%.

In our series of cases only two or 2.3% have been pronounced cured, one after a period of four years and another after two years. 21 cases or 23.8% were unimproved at the time of discharge. 10 patients or 11.4% died; two from perforation with peritonitis, three from severe toxemia, one from sepsis resulting after extraction of teeth, one from broncho pneumonia, one after appendectomy, one after appendicostomy and one after ileostomy. 55 cases or 62.5% were discharged as improved, many of these to return later with exacerbations. The best that we could say for the latter group of cases was that the patients were improved because the degree of involvement of the colon on sigmoidoscopic examination was less on discharge than on admission.

TREATMENT

Many varieties of treatment have been used in the attempt to cure chronic ulcerative colitis. Hare (23) feels that no treatment has been found that acts as a specific cure in an attack of this disease or that will prevent a relapse.

Rest in bed is essential when the patient is acutely ill, i.e. when there is hyperpyrexia, leucocytosis, increased sedimentation rate and very frequent bowel movements. Bargen (4) feels that when the acute infection has subsided the patient should be given some form of occupational therapy to distract his attention from the need of remaining near a toilet room.

Where the psychiatric background has been studied and psychological difficulties or emotional disturbances appear to be of etiological significance, Murray (9, 10), Rechad (30) and Sullivan (8) have found psychotherapy to be of distinct value.

DIET

Hurst (24), Bargen (4), Kiefer (22) and others specify various diets used in treatment. Suffice it to say that the ideal menu consists of a well balanced, high caloric, high vitamin diet, with foods digested mostly in the stomach and small intestine, and leaving as little residue as possible for the colon. Because of the rapid peristalsis there is little absorption in the colon and undigested food in the bowel is a source of irritation. Where hypoproteinemia is present, the protein content of the food should be increased. Synthetic preparations of all the vitamins are used orally, and parenterally when the patient is unable to retain them by mouth.

Many drugs are useful in alleviating the distressing symptoms of the disease but none has as yet been proven to be specific in its cure.

Some form of opium or codeine with belladonna will slow peristalsis and relieve abdominal cramps. Bismuth and kaolin will thicken the contents of the colon and reduce the number of bowel movements. Charcoal will absorb gases and relieve colic. Dilute hydrochloric acid should be given where there is achlorhydria. Iron is prescribed for the secondary anemia.

Stimson (25) advocates the use of sodium reioleate by mouth in order to detoxify the upper bowel, and as an irrigation in 1% solution in order to aid the elimination of toxic and infective products from the colon. Its use has not been attended with any improvement in our cases. Castor oil has been recommended for the same reason. Its use is to be condemned. Multiple perforations of the colon with a fatal peritonitis resulted in one of our patients.

Andresen and D'Albora (26), in addition to general methods of treatment, also use mercurochrome intravenously. They begin with a dose of 15 cc. of 0.5% solution and increase the dose at four day intervals sufficient to cause a febrile reaction of 101.5 to 102.5. They cite a number of cures.

The widespread use of sulfanilamide in infection has probably prompted many investigators to use this drug in the hope that it might be the long sought for specific. We have tried it in three cases, using 30 to 40 grains daily in divided doses for a period of two weeks and then repeating the course of treatment after a period of two weeks of rest. We have found no apparent benefit from its use. In fact it may have been responsible for an increase in the diarrhea of one of our cases and for an elevation of temperature in all three where such temperature was not present before its use.

Anti-amebic drugs such as emetine, etc., should be used where there is a question, no matter how slight, of the possibility of the condition being due to amebic colitis.

LOCAL TREATMENT TO THE COLON

Solutions of saline, potassium permanganate, acriflavine, mercurochrome, etc., have been used as colonic irrigations. The rationale of this form of treatment has never been proven. At their best, irrigations will merely cleanse the surface for only a few moments. The infection situated deeper in the coats of the colon cannot be reached by the irrigating solution. Kiefer (22), Hare (23) and Bergen (4) feel that the irritation caused by this form of treatment offsets whatever possible good can be obtained from its use.

Retention enemata have been found to be of value. Hurst (24) recommends the use of tannic acid solution, $\frac{1}{2}$ to 2 grains to the ounce, 1 to 1½ pints to be retained for ½ hour. Kiefer (22) uses a starch and opium retention enema to relieve tenesmus. Crohn and Rosenak (21) use neutral acriflavine (1:4000 parts of normal saline). Fradkin (27) used a mixture consisting of 20% kaolin, 10% mineral oil and 70% of a gel of aluminum hydroxide by retention enema in the convalescent patient where the stools were streaked with blood. As an adjunct to specific therapy this method aided in reducing the number of stools and healing the mucosa. Eyerly and Breuhaus (28) use a retention enema consisting of a three to five ounce mixture of kaolin and aluminum hydroxide in from three to five ounces of warm distilled water. Usually one but occasionally two retention enemata are given daily. The objection to the use of these enemata is the inability of the patients to retain them without marked discomfort for more than a few moments.

Soper (32) uses daily insufflations of calomel and bismuth subcarbonate and reports a number of cures

in his early cases of chronic ulcerative colitis. We found no improvement in three of our cases from this form of therapy.

SUPPORTIVE MEASURES

The intravenous use of saline and glucose is indicated in cases of dehydration and starvation accompanying marked diarrhea. In hypoproteinemia with its resultant nutritional edema we have found the use of acacia intravenously to be of value.

TRANSFUSIONS

Bergen (4) uses repeated transfusions of about 200 cc. of blood four to seven days apart to fight the toxemia in cases of severe sepsis and for the anemia and weakness following the loss of blood. Hurst (24) recommends transfusion when the hemoglobin falls below 70%. We have used transfusions in all of our toxic or anemic patients and have found them the best supportive measure to tide the patient over the acute phase of the disease.

SERA AND VACCINES

Hurst (24, 5) and Turner (11) feel that many cases, especially the early ones, respond to specific treatment with anti-dysenteric serum. Crohn and Rosenak (21) use polyvalent antidysenteric serum or typhoid vaccine intravenously. The latter feel that the beneficial results obtained are due to the production of protein shock.

Bergen (4) uses a concentrated serum prepared by immunizing horses against many strains of the diplo-streptococci found in the diseased tissues. This is administered intramuscularly in acute and chronic cases until improvement sets in. Following this a bacterin prepared as an autogenous vaccine from organisms found in rectal ulcers in each case is administered subcutaneously. It is given for several months in increasing doses from 0.1 to 1.5 cc. After a rest of several months it is repeated. Three or four such courses are administered or the vaccine is given until the patient is free of symptoms. After that an occasional course of vaccine is given for several years. Hare (23), Bassler (16), Hurst and Dukes (5) do not believe that Bergen's serum and vaccine are of any value. Alvarez (29) states "It is hard to understand why so many able physicians either stand cold before Bergen's achievements or else are actively hostile to his theories and statements of fact. Many men, when asked if, in trying to confirm Bergen's discovery of the diplococcus, they used his technique, admitted they had not. Few made a thorough going test of his serum and vaccine. Some did not use these measures, others only half heartedly, because they felt any foreign protein would work as well."

In our series of cases the diplococcus was isolated in 16 and the vaccine prepared and given to 11 patients. One was definitely cured and 10 have shown marked improvement. Typhoid vaccine was used intravenously in three cases, two of which showed no improvement and one slight improvement. Autogenous vaccines were prepared from the stools of 11 patients where no specific organism was isolated; four were improved, seven unimproved.

Bacteriophage prepared from the organisms found in the stool has been recommended by some authorities. Both stock and autogenous preparations have been used. They may be given orally, rectally or parenterally. Three of our cases were treated with

bacteriophage, one through rectal instillation and two by means of subcutaneous injections. Two showed no improvement. In one case a stock bacteriophage was used parenterally in conjunction with an autogenous vaccine. This patient has no recurrence after two years.

SURGERY

All evident foci of infection should be eradicated. Most medical authorities feel that surgery of the colon as a cure for chronic ulcerative colitis should be used as a last resort. Hern (12) feels that "internal anastomoses and the like are too stupid in their conception to be worth more than mere mention." Kiefer (22) feels that transverse ileostomy should be done in cases of extreme toxemia. Hurst (24) feels that surgery should be used only in the complications of chronic ulcerative colitis and that colectomy is the procedure of choice. Turner (11) feels that cecostomy should be done to put the colon at rest. Flick (31) reports a case of five years standing cured by total colectomy. Soper (32) reports six of his cases cured by this operation. One of our patients died after appendicostomy, another after ileostomy. One patient showed no improvement after cecostomy.

We advise against elective surgery in the presence of chronic ulcerative colitis. Two of our patients had appendectomies and three had hemorrhoidectomies performed during the course of the disease, all of which were followed by severe exacerbations. One patient died after an appendectomy.

SUMMARY

The recent literature of chronic ulcerative colitis has been reviewed.

An analysis of 88 cases has been presented.

The youngest patient was seven years of age, the oldest 70 years of age. There were 63 cases (72%) which comprised the groups between 16 and 40 years of age. There were 55 females (62%).

No specific organism was isolated in 63 cases (72%). The diplostreptococcus was isolated in 16 cases (18%), the enterococcus in 6 (7%), a green streptococcus in two, and a hemolytic staphylococcus in one.

Five cases gave definite antecedent histories of "nervous breakdowns."

There were 20 instances of recurrences with the following conditions: Seven with upper respiratory infections, one with pleurisy, five with pregnancy, one after tonsillectomy, one after removal of the teeth, two after appendectomy, three after hemorrhoidectomy.

Many complications were encountered, the most frequent being stricture of the bowel, polyposis, perianal abscess and fistula in ano.

In addition to general methods of treatment 11 patients received autogenous vaccines prepared from the stools of whom four were improved and seven unimproved. 11 patients received an autogenous vaccine prepared from the diplostreptococci isolated from the lesions in the colon of whom one was cured and 10 were markedly improved. Three received typhoid vaccine of whom two were unimproved and one improved. Three received bacteriophage of whom two were unimproved and one apparently cured, the latter receiving at the same time an autogenous vaccine prepared from the stool. Three received two courses of sulfanilamide none of whom were improved.

Surgery of the colon was attempted in three patients; cecostomy without improvement; appendicostomy and ileostomy, subsequent to which the patients died.

All patients with toxemia, hemorrhage or secondary anemia received repeated transfusions.

Two patients (2.3%) were cured, 55 (62.5%) were improved, 21 (23.8%) were unimproved and 10 (11.4%) died.

I wish to thank Miss Genia Rabinowitz, bacteriologist at the Beth-El Hospital, for the excellent microphotographs presented in this paper.

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The Vitamin B Complex and Functional Chronic Gastro-Intestinal Malfunction: A Study of Two Hundred and Twenty-Seven Cases

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DISORDERED function of the gastro-intestinal tract appears in animals deprived of vitamins A, B*, C, or D (1, 2). Diarrhea or constipation, spasm or atony may occur. Similarly, it has been recognized for years now that disorders of the gastro-intestinal tract are conspicuous in human nutritional deficiency diseases such as beri-beri and pellagra. In these diseases the factor involved is nearly totally deficient in the diet.

Much less is known and accordingly there is more difference of opinion regarding the incidence and signs of mild, but prolonged vitamin deficiency in humans. Thus the Vitamin Committee of the British Medical Research Council reported in 1932 (3).

"No convincing clinical evidence is available to show that the vitamin B complex determines the normal functioning of the human bowel, and until such is forthcoming it is unnecessary to assume that vitamin B deficiency is concerned in the production of the constipation so commonly met with among Western peoples."

Alvarez (4), though not quite so explicit, is inclined to a similar view. In his opinion disease due to avitaminosis is probably rare in American adults. Accordingly a condition as common as chronic gastro-intestinal malfunction can hardly be the result of vitamin deficiency. Morse (5), is of this opinion also.

Neither the Vitamin Committee nor the above authors have submitted in support of their view explicit descriptions of clinical or experimental investigations. The severity of vitamin deficiency which these authors had in mind is therefore uncertain. From the context it would seem that they meant severe deficiency as in xerophthalmia, beri beri, or scurvy. These diseases are, as these authors maintain, rare now among adults in the United States.

But the point at issue is to what extent are some common chronic ailments such as those of the gastro-intestinal tract the result of suboptimal vitamin intake over a long period. One of the first authors to stress the affirmative view here was McCarrison (2). But it must be admitted that his experimental and clinical observations dealt with severe deficiencies. This, possibly, was one of the reasons for the refusal of the Vitamin Committee to accept his view. Since the work of McCarrison, and in part stimulated by him, a number of reports have appeared in which a definite

connection has been shown between chronic gastro-intestinal malfunction in human beings and subacute vitamin B deficiency. Thus Fletcher (6) and Fletcher and Graham (7) presented X-ray evidence that disturbances of the colon such as loss of tone, decreased or absent haustral markings, and increased length, can be relieved by a high vitamin B, low carbohydrate diet. Marks (8) reported marked relief of constipation, improvement in appetite, strength and vigor in a fairly large number of patients following the daily ingestion of 15 grams of wheat germ daily. A similar experience in a smaller group of cases was reported by Montague (9). The results of an intensive study of two well-controlled cases were reported by Elsom (10). She observed that marked relief from anorexia, epigastric distress, constipation and asthenia were obtained following the administration of large doses of brewers yeast. The improvement was much less with purified single components of the B complex. Vorhaus, Williams and Waterman (11) reported a small group of cases in which constipation was relieved by large doses of crystalline vitamin B₁.

With the exception of those reported by Elsom none of the above patients were cases of obvious vitamin B deficiency. Presumably they had been living on the "usual American diet" which Alvarez and Morse consider supplies adequate amounts of all the vitamins. The results obtained by these investigators with large supplements of vitamin B indicate that there is a pathological insufficiency of vitamin B which is not as severe as frank beri beri or pellagra and that this condition is probably common, if one may judge from the prevalence of chronic constipation.

The study reported here was begun four years ago. Scrutiny of a number of diets selected at random found, similar to Eddy (12) and Marks (8), that the vitamin B intake of most people is little above the anti-beri beri protective level. For instance, few adult diets, even among the well-to-do, contain 400 International units of B₁ daily, which is twice the anti-beri beri level. To this is added, as a rule, a high carbohydrate intake which requires increased amount of B₁ (1, 13). The specific purpose of our investigation was to ascertain whether "functional" gastro-intestinal malfunction may be ascribed to any extent to a chronic partial vitamin B deficiency.

Though unaware of it at the time this study was a re-examination of the question on which the Vitamin Committee of the British Medical Research Council

*By vitamin B we mean, unless stated explicitly otherwise, the whole B complex.

had already given an opinion. It may be stated here that after four years of close observation of over 250 cases our findings disagree with the opinions of the Vitamin Committee, Alvarez and Morse. They support the view first emphasized by McCarrison, and the later corroboratory observations cited above.

The contribution we aimed to make to this controversial question was a closer study over a longer period of a larger number of cases than has yet been reported in this connection. The method of investigation employed was designed to meet the following requirements: 1. The diet, though adequate from a nutritional point of view, must be simple and practical enough to be carried out in the home; though standardized it must contain enough variety to satisfy a large number of cases; and not so rigorous that the

TABLE I

Summary of the effects of different nutritional treatment of 67 cases of chronic gastro-intestinal malfunction

Regime and Type of Case	Number of Cases	Number Improved	Number Not Improved
On regime alone without additional vitamin B supplement	67	18	49
Those not improved on regime alone subsequently given cereal vitamin B supplement	21	13	8
Those not improved on regime alone subsequently given liquid vitamin B supplement	28	19	9
Those not improved on regime plus cereal supplement, in whom the liquid vitamin B concentrate replaced the cereal	8	5	3
Final totals	67	55	12

patient will want to abandon it after a short trial. 2. The patients are to be studied in dispensary and private practice. Nevertheless the method of observation should yield approximately objective records.

The main difficulty was to obtain satisfactory objective records. Only cases with "functional" disturbances of gastro-intestinal function were accepted for study. By definition therefore there were no obvious significant signs. There were only symptoms—constipation, intra-abdominal pain, gas, a feeling of fatigue, etc. Radiograms of the gastro-intestinal tract did not yield any concordant instructive information. Some showed a spastic colon, others a dilated colon, in most the shape and emptying time were normal. The uniformity in these cases was in the symptomatology. Accordingly we decided to enlist the cooperation of the patient in observing the changes in his condition, especially as in any case the important information would be obtained from his answers to our questions. The uncertainty of this information was reduced, we feel, by the long period of observation, by our own periodic examination, by the concordance of the changes noted in a large group of cases under widely varying conditions, and by the method we employed (described below) for obtaining these records.

There are four main features in the regime insti-

tuted: (1) the provision of what may be called a balanced diet; except (2) that the carbohydrate content was reduced by the elimination of such "visible" sources as sugar, potatoes, white flour, etc.; (3) the provision in most cases of a high intake of vitamin B in the form of a special cereal described below or of a liquid concentrate; and (4) stopping the use of laxatives, intestinal lubricants, cathartics, and enemata.

The details of the regime and the management are as follows. Every patient was given the following instructions on a mimeographed sheet:

1. No bread, neither whole wheat nor white, no potatoes, neither sweet or plain, no pie, nor candy must be eaten.
2. Drink at least 1 pint of milk daily, 1 glass of orange juice or tomato juice, and 4 glasses of water. Eat at least 1 egg daily, not raw, best boiled for 3 to 5 minutes.
3. Eat a liberal helping daily of green vegetables, such as spinach, carrots, string beans, broccoli, lettuce, asparagus. Do not cook vegetables in a lot of water. Do not throw away the water. Mix it with your food.
4. If you feel that you want to eat more, fill up on milk, meat, and vegetables.
5. Do not take enemata, laxatives, headache medicines, or other remedies except as directed.

Most of the patients received a vitamin B supplement consisting of 100 grams (dry weight) of a special wheat cereal. The technical name of this cereal among millers is "the scalp of the sizings." At present its composition is not quite uniform. It contains on the average 10 to 15 per cent of germ, and the finely ground inner branny layers. The bulk of it consists of protein and starch of the adherent endosperm. This cereal was found to contain from 5 to 10 International Units of vitamin B₁ and about 3 units of the B₂ complex per gram of dry weight*. Our instructions for the use of this cereal are: 1 standard measuring cup of dry cereal cooked with 1 to 2 parts of water in a double boiler for 15 minutes to ½ hour; to be eaten with whole milk, preferably all at breakfast, the remainder may be eaten at luncheon. This is a large quantity of cereal; but most of our patients had no difficulty after about a week in taking this quantity at breakfast. Those for whom it was too much were advised to take some of it as muffins or pancakes.

This cereal fraction is the cheapest, palatable source of the vitamin B complex available at present. It keeps well (for several months in a cool place). It is more palatable for most of our patients than other cooked cereals. It contains a remarkably large amount of the vitamin B complex.

The restriction of carbohydrates in the above regime is based on the fact that normal carbohydrate metabolism is dependent on vitamin B₁ (1, 13). Accordingly the requirement of this vitamin is partly dependent on the extent of the carbohydrate metabolism. If the gastro-intestinal difficulties of our cases were in part at least a consequence of prolonged mild or subacute vitamin B deficiency, it seemed a rational procedure to increase the effectiveness of the vitamin B ingested by restricting the carbohydrate intake. We have estimated that even in our prescribed diet carbohydrate contributes about one-half of the caloric value.

*We are indebted to Mrs. M. K. Dimick of the Vitab Company, Berkeley, for the biological assay of this cereal. The B₂ complex was estimated before it was fractionated into flavine and other components.

TABLE IIA

Numbers of cases complaining of different symptoms and the numbers markedly improved on the prescribed diet plus the cereal supplement

Total Number of Cases	Where the Cases Were Observed;	Constipation		Abdominal Pain		"Gas"		Nausea		Mucus in Stools No. of Cases
		No. of Cases	Improved	No. of Cases	Improved	No. of Cases	Improved	No. of Cases	Improved	
23	Dispensary A;	21	20	20	17	21	11	8	4	5
32	Dispensary B;	25	23	25	23	27	13	8	5	10
26	Dispensary C;	26	26	19	18	20	16	1	0	6
31	Dispensary D;	31	30	20	19	25	15	11	9	11
48	Private practice	48	47	28	26	39	21	7	5	12
160		151	146	112	103	127	75	35	23	44

Age Distribution in

per cent of total:

Under 10 10-19 20-29 30-39 40-49 50-59 60-69 over 70
1 2 10 16 20 19 10 2

Females 62 per cent.

No effort was made to reduce the amount of roughage in the diet. The pureeing of vegetables was not recommended; and there is some bran in the cereal. This bran, it must be noted, is much more finely divided and lighter than the commercial varieties of bran, which are derived from the outer branny coats. Many of our cases had been living on bland diets, with pureed vegetables, etc., following courses of sanatorium treatment for "colitis." These were at first alarmed at the amount of roughage in the diet prescribed. Nevertheless only one of more than 250 cases found the diet irritating.

Each patient was given a mimeographed questionnaire sheet on which he recorded daily his condition under the following headings:

Bowel movements, number and character; abdominal pain, character and location; gas, bloating, belching, passage by the bowel; blood or mucus in the stool; nausea; vomiting; appetite; nervousness; fatigue; headache; cold hands and feet; other disturbances or illnesses; exercise taken; any unusual trip or entertainment; sleep, time of retiring and of rising; have you omitted from the diet any of the prescribed items?

The form of the sheet provided for daily answers

TABLE IIB

Numbers of cases complaining of different symptoms and the numbers markedly improved on the prescribed diet plus the cereal supplement

Total Number of Cases	Where the Cases Were Observed;	Mucus in Stools Improved	Anorexia		Headache		Nervousness		Asthenia or Marked Fatigue	
			No. of Cases	Improved	No. of Cases	Improved	No. of Cases	Improved	No. of Cases	Improved
23	Dispensary A;	4	17	14	13	8	15	9	20	17
32	Dispensary B;	6	16	13	18	14	19	7	20	14
26	Dispensary C;	5	13	10	7	3	9	3	27	15
31	Dispensary D;	7	26	20	19	12	29	10	20	16
48	Private practice	7	16	12	29	10	27	14	38	29
160		29	88	69	77	47	91	43	119	80

Age Distribution in

per cent of total:

Under 10 10-19 20-29 30-39 40-49 50-59 60-69 over 70
1 2 10 16 20 19 10 2

Females 62 per cent.

for seven days. The patient presented himself with these records at intervals which varied from one to four weeks. He was then interrogated regarding his condition and his answers; and his own questions answered. He was examined whenever changes in his condition or his complaints seemed to call for it. It should be noted here that the observations on the number and character of the bowel movements may be considered as approximately objective.

We eventually possessed a detailed account of the day to day state of the patient over a long period—in some cases for as long as four years. Our estimate therefore of whether the patient was better or worse in any respect is not based on the patient's statement at any one time, but on a comparison of the records over a long period written each day. The patient had, of course, after a few months forgotten the details of his early records. Hence his later written statement of his condition was relatively independent of his opinions and feelings some months previously.

The cases chosen were from dispensary and private practice. We felt that although a small group of patients confined to hospital afforded an opportunity for better control and intensive study, the conditions are artificial. Any improvement obtained might be maintained only while the patient is living in the special conditions of the investigation. On the other hand any amelioration which had set in while the patient was living in his usual environment carrying his burden of social obligations, not only was likely to be more permanent, but the treatment and the investigation could be carried on for a longer time and with many more cases.

Some of the tentative diagnoses with which the patients were referred to us were: spastic constipation, atonic constipation, chronic gastro-enteritis, colitis, chronic arthritis, hypertrophic arthritis, polyneuritis, epilepsy, malingering, hysteria associated with constipation. In all of the cases accepted for this study the derangements of the gastro-intestinal tract, as far as we could ascertain by clinical, laboratory, and radiological examination, were of the "functional" type. This selection was made, as stated above, to test the hypothesis that a contributory factor in these cases is long standing, partial vitamin B deficiency.

The results obtained summarized in Tables I and II appear to verify this hypothesis. They are not definitive proof because of the difficulty, which the selection of cases entailed, of obtaining thoroughly objective records. On the other hand our records and observations are sufficiently extensive, well checked and concordant, to be taken as indicating that chronic partial vitamin B deficiency (or suboptimal intake) is probably one of the factors "in the production of the constipation so commonly met with among Western peoples," and of other signs and symptoms of chronic gastro-intestinal malfunction in adults.

Before discussing the main body of our results which are summarized in Table II we shall describe first those obtained in a group of 67 cases (not included in Table II) where an effort was made to appraise the relative importance of the management of the case, the character of the diet, and of the vitamin B complex.

These 67 cases were first given the diet alone without the cereal or other vitamin B supplement. Eighteen of these obtained such marked relief on this regime that no other treatment was necessary. In this group,

as in all the others where definite improvement was obtained, it occurred quickly, often within 2 weeks, and in no case later than 6 weeks. The constipation corrected itself first, later the dyspepsia and abdominal discomfort or pain, then anorexia disappeared. Gradually a marked improvement in the sense of general well-being, diminished fatigue or asthenia were noted. Gas was the most persistent symptom and the one from which least relief was obtained and least often.

Twenty-one of those who had shown no improvement after 2 months on the diet alone now received the cereal supplement. Thirteen of these were definitely improved within 3 months.

The diet of the remaining 36 cases, 28 of whom had shown no improvement on the diet alone, and 8 no improvement with the cereal supplement, was now enriched by a liquid concentrate of rice polishings.* 20 cc. were taken daily, divided into three equal portions before meals. This provided at least 1000 International Units of B₁, 250 units of B₂, and a large (but at present undetermined) quantity of the B₆ complex and the antipellagric factor. Of the 28 cases who had obtained no improvement on the diet alone 19 now became markedly better within 3 months. Five of the 8 who had obtained no noticeable benefit from the cereal supplement became free of most of their symptoms within a few months after the cereal was replaced by the liquid concentrate.

Twelve of the 67 cases obtained no significant benefit from our therapy.

In the group taking the liquid vitamin concentrate the first improvement noted was again the correction of constipation. This appeared within 2 to 4 weeks, and occurred in all of the 24 cases of this group who obtained any improvement whatever. Anorexia disappeared in 18 of this group, and dyspepsia in 20. Improvement in the feeling of strength and in general well-being was commented on by all of the 24.

A summary of the results obtained in this group of 67 cases is given in Table I. If this group is a fair sample it appears that approximately one-quarter of the cases of "functional" chronic gastro-intestinal malfunction can be relieved of most of their symptoms simply by providing a well balanced diet and stopping the use of laxatives. Other factors contributing to this improvement may have been psychological influence and the effects of generally improved hygienic circumstances resulting from regular medical questioning and examination. In two-thirds of the cases these measures were inadequate. In more than half the total number of cases definite general improvement was established only after the ingestion for some months of rather large amounts of supplementary vitamin B. The results obtained with the liquid concentrate argue against the importance of bulk or roughage in the diet or in the cereal.

A group of nearly 200 cases received the cereal supplement from the beginning. The records of 160 of this group are summarized in Table II. The forty odd remaining cases were omitted from the table because the records were incomplete; but the results appeared to be essentially the same as in those recorded. Table II does not include the cases in Table I. The age and sex distribution in all our cases is given at the foot of Table II. The statistical distribution of the results appears to be unaffected by either the age or sex of

*This concentrate was generously supplied us by the Vitab Products, Inc., Berkeley, the manufacturers.

the patients. It will be noted that essentially the same results were obtained whether the patients were treated in private practice or in dispensaries.

Relief of constipation was obtained most frequently. Next in order of frequency was relief from abdominal pain.

The order in which the symptoms were relieved in an individual case was the same in these groups as in the 67 cases discussed above: constipation (in most cases within 2 to 4 weeks), abdominal pain, appetite, headaches, the feeling of fatigue. "Gas" was again the most persistent complaint.

It may be noted here that the observations regarding constipation may be considered as objective ones. Certainly they are least influenced, as observations, by subjective bias. Yet it is precisely here that the most striking improvement was recorded in every group.

Two changes observed call for some additional comment. In 30 cases there was a notable improvement in the complexion. This clinical observation is interesting in the light of the later demonstration that the vitamin B complex contains at least two anti-dermatitis factors (14).

To our mind the most important improvement noted, and it is inadequately recorded in the table, was in the state of well-being. Six who were on the Relief Roll because they felt too ill or too weak to work, later voluntarily applied for work. A similar change was observed by Marks.

We obtained some evidence that continued ingestion of relatively large amounts of vitamin B is required. Eight patients were selected who had shown no improvement on the diet alone; 3 had become symptom free with the liquid concentrate, 5 with the cereal. After they had been free of symptoms for 3 months the vitamin supplements (liquid concentrate or cereal) were withdrawn. In every case the original symptoms returned within 3 months. On the resumption of the vitamin B supplement they again became symptom free.

In five cases who had become free of symptoms while taking the cereal the same weight of pure wheat germ was substituted for two months. This substitution gave approximately 50 per cent more B₁ at the cost of a large decrease in the other members of the B complex. In all five cases symptoms reappeared after one month and became worse. These disappeared again when the use of the cereal was resumed. This experience suggests that other components of the B complex besides B₁ are important in the alleviation of gastro-intestinal malfunction. A similar observation was made by Elsom.

We have had 3 cases of chronic diarrhea in which all the common causes had previously been excluded. One of these failed to obtain any benefit from the treatment described above, 2 were completely cured.

The history of one of the latter two cases briefly is as follows:

Male, aged 52, during the previous 18 months had had 3 to 6 bowel movements daily with the passage of considerable mucus; generalized abdominal pain, and tenesmus. He had lost 28 pounds and had become markedly anæmic. He was referred with a diagnosis of chronic, non-specific, ulcerative colitis.

One month on the diet alone, followed by 6 weeks with the cereal supplement brought no improvement. Within a month after the cereal was replaced by the liquid vitamin B concentrate progressive improvement

set in. Within 2 months he was having 2-3 semi-solid bowel movements daily, was free of abdominal discomfort, and had gained 10 pounds. After 5 months he was having one normal bowel movement daily, had gained another 12 pounds, his complexion was improved, and his former strength had returned.

The other case became free of symptoms on the diet with cereal supplement.

DISCUSSION

It is now well established that there are what may be called physiological variations in the minimum vitamin B₁ requirement of adults. The minimum quantity of this vitamin required to prevent beri beri increases with weight, metabolic rate (fevers, hyperthyroidism), exercise, pregnancy, lactation, and the extent of carbohydrate metabolism. Some of these relations have been incorporated in a quantitative expression by Cowgill (15).

The optimum amount of vitamin B, i.e. the amount which affords optimum growth in the young, good health and the longest postponement of senility in the adult, may be four or five times as large as the minimum amount required to prevent beri beri. Sherman and Ellis (16), measuring differences in rates of growth and in the postponement of senility at different levels of vitamin B₂ (G) intake, are of the opinion that the optimum amount was not attained in their rats with five times the minimum protective dose.

A valuable study of this point was made by Drummond (17). He maintained rats on a level of vitamin B intake slightly below that required for normal growth. These animals were compared with normals, over a period of more than two years. This slight reduction in vitamin B intake had a marked influence on the adult life of the rat. Though the animals on the deficient diet attained adult size in practically the normal time, only 38 per cent survived two years compared with 64 per cent of the animals who obtained the larger amount of vitamin daily. The females in the deficient series had 14 pregnancies compared with 94 in the normal series. Seventy-six were born in the deficient series, and of these 16 per cent survived one month, whereas in the normal series there were 635 born with 88 per cent surviving one month.

This difference between minimum and optimum levels of vitamin B intake also occurs in humans. None of the subjects of the present study showed signs of beri beri, polyneuritis, pellagra, or any other evidence of acute vitamin B deficiency. The improvement in gastro-intestinal function following the ingestion of large amounts of vitamin B showed that they were subsisting on a suboptimal vitamin intake. The factors enumerated above, which determine the minimum requirement of vitamin B, probably enter here also and also influence the optimum requirement.

The present study also brought out what may be called a constitutional factor affecting the level of optimum vitamin intake. Some individuals require more vitamin B for good health than others. Thus in our first series of 67 cases about 25 per cent were relieved of their symptoms simply by the cessation of the laxative habit, and the provision of normal servings of fresh vegetables, citrus fruits, milk and eggs. For a larger number of cases this simple regime was inadequate. These individuals required a richer vitamin B intake than is provided in the ordinary good

diet. At present we can only speculate on the reasons for this variation in the level of the optimum vitamin B intake.

Another point which warrants some emphasis at present is the distinction between the use of large amounts of the whole B complex and of highly purified single components. Vitamins B₁ and B₂ (G, flavine), and the anti pellagic factor nicotinic acid, are now available in the crystalline state commercially. There are indications from the experimental work on animals and in Elsom's and our observations on humans that in most cases the whole B complex is superior therapeutically to any single fraction. There is also the obvious and important economic reason for preferring the whole B complex as it is found in foods to any highly purified single component. In this connection we would draw attention to the usefulness of the cereal fraction we have employed. It is rich in the vitamin

B complex, palatable, available wherever wheat flour is made, and cheap.

SUMMARY

1. A study is presented of the treatment by a dietary regime of 227 cases of chronic gastro-intestinal malfunction. The cases reported were studied for not less than three months, most for more than a year, and some for as long as four years.

2. Marked benefit was obtained in nearly all of these cases from the continued ingestion of large amounts of the vitamin B complex.

3. We have interpreted this result as indicating the existence of a widespread, partial vitamin B deficiency in humans, i.e. that many, if not most, people require for normal gastro-intestinal function several times the minimum amounts of the vitamins required to prevent severe deficiency diseases such as beri beri and pellagra.

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The Vitamin C Content of Certified Milk at the Time of Consumption

By

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and

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MANY investigators have contributed a vast amount of knowledge on the subject of the vitamin C content of milk. Most determinations, however, have been made immediately or very soon after the withdrawal of milk from the cow. This report involves a study of the actual vitamin C or ascorbic acid content of certified milk at the time it is consumed in the home.

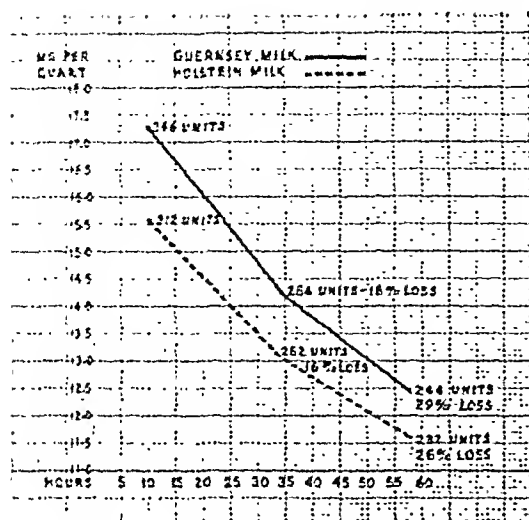
The effects of breed characteristics on vitamin C in milk were not a part of the study. However, as indicated in the accompanying chart, our findings are in close agreement with those of Russel, Rasmussen (1), and others.

The feeding of the cows was carried out in the customary manner. When corn ensilage was discontinued there was no appreciable change in the vitamin C content of the milk. The addition of orange meal to the grain feed made no apparent difference in the

ascorbic acid content of the milk. The catalytic and oxidizing factors involved in the preparation of orange meal probably account for its lack of vitamin C value.

Practically all stages of lactation were represented in the 108 cows that were used in the study. The milk was drawn into stainless steel buckets, aerated and cooled to 38° F. and held in refrigerated stainless steel vats until 150 gallons of milk were collected which required an average of approximately 65 minutes. Samples of Guernsey and Holstein milk were taken from the regular run of milk between two and three a.m. on Mondays, Tuesdays and Wednesdays for a period of ten weeks, starting in January. Samples were collected at the dairy farm and were hauled without refrigeration to the laboratory, a distance of 20 miles.

In the study an effort was made to simulate a con-



dition that would cause a greater loss of vitamin C than would occur in the handling of milk in the average home.

Vitamin C determinations were made when the milk samples had reached the respective ages of 10, 34 and 58 hours. The samples were permitted to stand for 2 hours daily at room temperature and at all other times were held at 43° F.

The vitamin C determinations were made in the following manner: 10 cc. of milk were treated with 10 cc. of 16% trichloroacetic acid solution to precipitate the proteins and 6 cc. of 10% metaphosphoric acid solution to preserve the ascorbic acid. The latter precaution was taken to protect against losses through interruptions. The mixture was permitted to stand for 20 minutes after which the supernatant liquid was removed by centrifuging at 1500 R.P.M. for five minutes and decanting. The precipitated residue was not washed. Titrations were made with a standard solution of sodium 2,6 dichlorobenzenoneindophenol from which a stock solution was used for five days only. From the stock solution a fresh dye was made each day and standardized against a N 100 iodine solution and also against ascorbic acid (La Roche). A

total of 720 titrations were made. The accompanying graph indicates our finding.

The maximum permissible age of certified milk is 30 hours at the time of delivery to the consumer (2). In Los Angeles the milk from the dairy farm where the samples were taken is delivered at an age from 10 to 24 hours. Allowing 10 hours in the home for consumption, the maximum age of the milk would approximate 34 hours, at this age the average minimum vitamin C content of the Holstein milk would approximate 13.1 mg. per quart (262 international units) and that of the Guernsey 14.2 mg. per quart (284 international units).

The Council on Pharmacy and Chemistry of the American Medical Association state: "The claim that a food is valuable because of its vitamin C content should be permitted only if it provides a daily intake of at least 250 units of vitamin C" (3).

Therefore, the certified milk from the dairy farm where these samples were taken may be said to be "a valuable food because of its vitamin C content" if one quart of milk is consumed daily and the same standards of production continue. Because of the great variation in the vitamin C content between different types of milk, no claims should be made for any milk unless such claims are substantiated by laboratory determinations.

The milk used in this investigation may be considered as a highly desirable safety valve in cases where the infant or child has been deprived of citrus fruits or their juices. No attempt, however, should be made by milk producers to discourage the use of orange or lemon juice.

SUMMARY

720 titrations in determining the vitamin C content of certified milk from 108 cows indicate that this milk on which the determinations were made may be considered "a valuable food because of its vitamin C content."

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Cyst of Gastro-Colic Omentum

By

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WHILE there are comparatively numerous reports of cysts of the mesentery, there are not many recorded cases of cysts in the omentum. This is a report of an enteric cyst in the gastro-colic omentum.

Four main varieties of cystic tumors appear in the

peritoneum, mesentery and omentum: Lymphatic or chylous cysts, enteric cysts, urogenital cysts and dermoids or teratoids.

Enteric cysts form single or multiple large or small cysts lying usually along the lower end of the ileum, in the wall of the intestine, at the point of Meckel's diverticulum (Boh), in the mesentery, or near the



Fig. 1. Enteric cyst anterior to and attached to gastro-colic omentum between stomach and splenic flexure of colon.



Fig. 2. Low power magnification 100X. Cyst wall showing single layer of endothelial cells at top, stroma, and intestinal acini in lower portion.

navel (Wyss) When originating within the muscular wall of the intestine, they usually remain connected with this organ and are enclosed by a muscular wall. The cavity is usually single and the contents are mucinous, colorless, yellowish or brownish fluid. The wall resembles that of the intestine, and may contain smooth muscle, mucosa, crypts, lymphoid tissue, and a lining of cylindrical or cuboidal or stratified epithelium (Colmers). The epithelium may show papillary proliferation. Both cylindrical and squamous cells may be found in the same cyst.

Roth and Hennig found a large cyst in the mesentery and one in the posterior mediastinum, both in infants. Sanger and Klopp, in a newborn infant, found 5 cysts, in the walls of two of which were portions of liver tissue. Honl has reported 2 remarkable cases of multiple enteric cysts in which there were 37 and 89 small cysts lined by intestinal mucosa (1).

B. Schwarzenberger, in 1894, reported a case of multiloculated cyst of the omentum, discovered at operation, in which there was clear fluid, Sp. Gr. 1016 (2).

During life, large omental cysts may simulate a loculated tuberculous peritonitis or an ovarian cyst. Other conditions that must be considered in the diagnosis are: Lipomata, mesenteric and pancreatic cysts, aortic aneurism, and large cysts of the spleen (3).

In this case reported, had the cyst enlarged, it would have produced pressure on the stomach or colon, with resulting symptoms.

This case is from an autopsy done at the Philadelphia General Hospital.

The patient was a female, black, age 49. The clinical diagnosis was complete perineal tear, with vesico-vaginal and recto-vaginal fistula, arteriosclerosis and myocardial degeneration. Abdomen showed a small umbilical hernia. There were no palpable masses and no areas of tenderness. The cyst was not diagnosed during life.

Autopsy Findings (Anatomical Diagnosis): Parenchymatous degeneration of myocardium; pulmonary

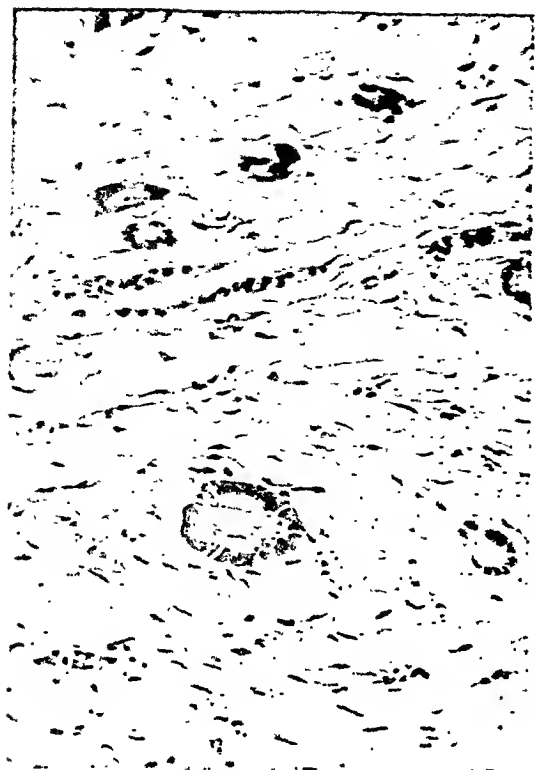


Fig. 3 High power magnification 200x Cells of columnar epithelium arranged in acinar formation. Stroma shows numerous fibroblasts.

emphysema, congestion, edema; chronic atrophic splenitis, arteriosclerosis of spleen; pyelonephritis, nephrosclerosis; urinary bladder, acute suppurative cystitis

secondary to vesico-vaginal fistula; recto-vaginal fistula; congestion, cloudy swelling and arteriosclerosis of liver; omental cyst.

Omentum: In the gastro-colic omentum, between the stomach and the splenic flexure of the colon, there was a circumscribed cystic mass, measuring 5 x 4.5 x 4 cm. The cyst was spheroidal in shape and unilocular. The cyst wall was semi-transparent, about 1 mm. in thickness in most areas, slightly thicker in other areas. From the outer surface it appeared light bluish purple in color. The substance within the cyst was gray and semi-solid, gelatinous in nature. The cyst did not seem to produce any pressure on the surrounding viscera. There was a general ptosis of the intestines, the transverse colon being below the level of the umbilicus. The cyst extended from the stomach to the splenic flexure of the colon.

Microscopically, there is a single layer of endothelial cells lining the cyst wall. The stroma shows mucoid degeneration and contains many fibroblasts. Cells of columnar epithelium are arranged in acinar formation. They resemble bile ducts.

Because there are some intestinal acini in the wall of the cyst, this is an enteric cyst derived from the dilated acini of a heterotrophic enteral gland (4).

SUMMARY

Because of its rarity, an enteric cyst of the gastro-colic omentum is reported, having been discovered at autopsy. This should be considered in the differential diagnosis when a patient is presented with a mass in the upper abdomen.

The author is indebted to Dr. Lawrence W. Smith for assistance in histologic diagnosis.

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The Early Diagnosis of Non-Tropical Sprue, with a Note Upon Its Familial Incidence*

By

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NON-TROPICAL sprue is a disease which is diagnosed both less frequently and later than should be the case. Perhaps explanation for this fact, in part, is the similarity which exists between the onset of sprue and mild enteric infections. More important, however, seems the fact that the clinical picture of early sprue is so markedly different from the usual or classical accounts of this disturbance. In early sprue the outstanding characteristic is increased frequency of bowel movement. In the classic type of sprue the very frequent bowel movements are accompanied by

emaciation, anemia, fatty stools and a host of other general abnormalities. In early sprue prolonged general discomfort of the patient is unnecessary, and for this reason it seems that this disease is worthy of prompt recognition and therapy.

As far as is known, the family reported herewith is the first one on record. A priori, if sprue is the result of insufficient production of some specific hormone, then as in the case of diabetes mellitus, it is not unusual to find a high familial incidence in some cases. Increased frequency of diagnosis probably will bring to light many more of these families.

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Submitted October 20, 1935.

LITERATURE

Although Snell reports that more than 100 cases of non-tropical sprue are on record, practically all of these cases are of the classical type. As discussed by Hanes and McBryde, for instance, they all include steatorrhea with or without bone changes and anemia. The cases of the series reported here differ from these classical cases in that the abnormalities are confined chiefly to the intestinal tract and there is no essential change in other organs nor systems.

CASE ABSTRACTS

Case 1. L. T. M., a 30 year old white male, was seen first in September, 1936, complaining of "nervous diarrhea" for the past three to four years. During childhood and until onset of the present illness the patient's bowel movements were normal. No history of residence in tropical climate. No other members of family troubled with similar type of disturbance.

Since onset of the illness the patient's bowels have moved three to five times daily. There is always considerable gas, frequently the stools are liquid and bowel movements must occur quickly once the impulse has been noted. Occasionally, for a period of one or two days, movements seem to return to normal. When diarrhea is maximal then there is a rather continual "nervous," "unsettled" feeling in the epigastric and mid-abdominal regions.

Physical examination revealed no essential abnormalities of the eyes, heart, lungs, chest and abdomen. Erythrocyte, leucocyte and hemoglobin values were normal. Fluoroscopic examination of the gastro-intestinal tract revealed rapid peristalsis and very little of the barium remaining in the terminal portion of the bowel at the end of five hours. Basal metabolic rate determination was -18.

Since 2-1 cc. ampules of a concentrated liver extract have been administered, at approximately ten day intervals, the patient has been practically free of the disturbance. The bowel movements have been kept to one, occasionally two formed stools daily. There was freedom from the nervous uneasy feeling in the epigastrium, and the patient was able to have bowel movements at his leisure.

Case 2. B. W., a 36 year old white female, first noted the onset five or six years ago of "bilious-like spells." Beginning at first as a "sick headache," each attack became increasingly more severe. The earlier attacks were characterized by onset of chills, then a nauseated feeling and finally a "terribly weak" feeling before the bowels moved. On most occasions the patient vomited and had no bowel movement simultaneously.

As the attacks progressed bicarbonate of soda was taken with increasing frequency for the uncomfortable feeling in the abdomen. One-half teaspoonful of milk of magnesia caused marked exacerbation of the diarrhea, the bowels moving approximately every five minutes for half a day.

With sedatives and relief of a certain degree of financial stress at home, the patient's condition improved somewhat with the years. Symptoms which have persisted, however, include rumbling, gushing sounds, and sensations in the abdomen and an uncomfortable sensation in the abdomen after eating. Occasionally there was constipation for a period of 24 hours; this, in turn was followed by 2 days of normal bowel movements during which time all traces of rumbling sensation disappear. The periods of constipation are believed by the patient to be due to omission of fruits and vegetables from the diet and the use of toast, macaroni, potatoes and fresh bread.

Bowel movements were noted as "bright orange" during periods of diarrhea, but are dark brown during periods of normal bowel movements. Rather frequently canker sores occur in the patient's mouth, but the frequency of occurrence of these has decreased since extraction of practically all the teeth.

Physical and laboratory examinations were essentially

normal. Fluoroscopic examination of the gastro-intestinal tract showed increased rapidity of movement of the barium meal. Specimens of stool revealed no definite abnormalities. More recently a mild hypochromic anemia has developed.

The familial aspects of this case are as follows: The patient has 3 sisters and 2 brothers. One sister is suffering from "colitis." Her symptoms are more severe than are those of our patient. She experiences more pain and more feeling of "congestion," while bowels move regularly three times daily.

The remaining sisters are living and well and their intestinal tracts apparently function normally. However, the son of one of these sisters, has "stomach trouble." His symptoms are similar to the above and hospital study has revealed no organic disease.

One of our patient's brothers also has "stomach trouble," characterized particularly by increased frequency of bowel movements. X-ray studies likewise revealed increased rapidity of passage of barium through the intestinal tract.

A second brother is living and well. Of the patient's four children, the two daughters, aged 9 and 14, are perfectly normal. One son, four years of age, complains at regular intervals of abdominal pain and discomfort. Symptoms persist for one week, then are absent for one month, on the average. Even during "quiescent" intervals the child never has less than two bowel movements daily. The mother emphasizes the fact that she "never remembers giving the child a cathartic."

A second son, 16 years of age, has experienced at irregular intervals, severe attacks of abdominal pain and diarrhea, but his mother has been unable to have this condition studied further.

Case 3. S. D., an eighty year old white female, noted rather insidious onset of diarrhea. Dietary intake was for the most part voluntarily limited, but certain additional restrictions were the result of attempts to control a discomforting arthritis. There were few symptoms associated with onset of the diarrhea. For the most part, the bowel movements were watery and occurred as often as eight to ten times in 24 hours. Powders given for the control of diarrhea were only partly effective, but there was a good response to codeine sulfate. Oral liver extract in moderate doses, together with an increased intake of beef and liver has relieved the diarrhea somewhat. Intramuscular liver extract plus the more normal diet made both powders and opium derivatives unnecessary.

Gastro-intestinal X-ray examination, done prior to the control of the diarrhea, revealed the usual increased rapidity of passage of barium through the gastro-intestinal tract together with smoothing of large bowel markings.

Case 4. A. M., a 42 year old white male, was seen first in July, 1937, because of what appeared to be a mild attack of gastro-enteritis. The symptoms subsided within several days following the use of bismuth subnitrate and codeine sulfate. Two weeks later the patient noted a recurrence of the diarrhea with semi-formed stools. There was no steatorrhea, nor dietary change which influenced the frequency of bowel movement. Additional symptoms included a generalized uncomfortable feeling throughout the abdomen and at times this feeling became very marked only to be relieved by movement of the bowels. Gastro-intestinal X-ray series showed increased rapidity of passage of the barium through the small and large intestines. Following intramuscular injection of 2-1 cc. ampules of a concentrated liver extract, the patient was entirely relieved of symptoms for a period of ten days. Subsequent injections of 1 cc. liver extract have been administered at intervals from eight to ten days with complete freedom from symptoms and intestinal abnormality.

DISCUSSION

The significant clinical characteristic of non-tropical

sprue is increased frequency of bowel movement. In the absence of fever, blood or mucus in the stools, it is the diagnosis of choice until proved otherwise.

The diagnosis of early non-tropical sprue, or preferably early sprue occurring in temperate climates, is made by relying practically entirely upon symptoms elicited by the case history. Increased frequency of bowel movement, abdominal discomfort, passage of liquid or semi-solid stools, exacerbation of the condition after ingestion of certain foods all are points of especial importance in the diagnosis. Abnormalities such as gastro-intestinal lesions, anemia, or stentor-rhea, if obtained during laboratory study of the case are indicative of the classic or fully developed stage of the disease.

The onset of diarrhea apparently may occur at any age in or beyond childhood. The disturbance seems most characteristic, however, when it occurs in young adults. The patients usually seem to have experienced sporadic attacks before the disturbance begins in earnest. Once the disease has begun, the abdominal discomfort becomes a common feature.

There is general agreement among patients with this disease that a sensation of inward abdominal nervousness is a prominent feature. Occasionally this is relieved by the bowel movement; occasionally it is accompanied by an additional sensation of rumbling and gushing within the abdomen.

In all of the cases here reported the stools are characteristic. For the most part they are soft or watery and light yellow in color. It is to be noted that this appearance is in sharp contrast to the oily, greasy, foamy, foul smelling stools of sprue in the advanced or classic stage. In the early sprue cases, despite the rumbling sensations in the abdomen there is very little discomfort from the passage of gas by bowel, and the patient only rarely complains of foul smelling gas.

Exacerbation of the disturbance after certain foods, makes one think of the possibility of an allergic condition being responsible for the disturbance. Undoubtedly this reaction to certain foods does occur, and perhaps is associated with onset of the disturbance originally. However, substitution of beef, liver, and buttermilk for vegetables in the diet result only in slight improvement if liver extract is not given. The fact that vegetables are tolerated well after the intestinal disturbance has been eliminated by injections of liver extract, makes food allergy only a supplemental factor.

The differential diagnosis of early sprue involves chiefly disturbances localized to the gastro-intestinal tract. If the patient is seen soon after onset of the disease a low grade enteritis from the dysentery group of organisms or from amebae is foremost among the confusing diseases. Usually with inflammation of the intestine, in these latter cases there occurs fever of varying degrees. Also blood and pus soon appear in the stools if the inflammation is very marked. Cultures of the stools reveal the offending agent. If the enteritis is the result of infection with protozoa then microscopic examination of fresh specimens of stools will reveal the invading agent. Sigmoidoscopy, in addition to allowing inspection of the mucosa of the lower bowel frequently also facilitates collection of material for examination.

Carcinoma of the intestinal tract must be ruled out before the diagnosis of early sprue can be made. It seems not unlikely that a gastro-colic fistula for

instance, resulting from carcinoma could simulate early sprue for a period of time. As the carcinoma progressed, its presence undoubtedly would become clearly evident. Gastro-colic, gastrojejunal or other fistulae as the result of surgical manipulations within the abdominal cavity usually are readily enough recognized from the history of abdominal operation and the findings upon fluoroscopic examination.

The progress of barium taken by mouth and observed beneath the fluoroscope is exceedingly rapid in sprue, once it has left the stomach. Usually in only three to four hours the head of the column of barium is found in the sigmoid. Not infrequently moderate amounts of the barium have been eliminated by this time.

TREATMENT

As regards treatment, liver extract in concentrated purified form is very effective if administered intramuscularly. Relief comes almost within two to three days after the first injection. In some instances, particularly very mild cases of early sprue, constipation results from administration of the liver extract. Variations in the amount of liver extract required can be met only by trial adjustment of both the amounts injected and the frequency of injection. Ordinarily one to two cc. of concentrated liver extract will protect against the disturbance from five to fifteen days. Within these limits it is well to let the patient judge the frequency of injection by the sensations which appear in the abdomen, together with frequency of bowel movement and consistency of the stools.

FAMILIAL INCIDENCE OF SPRUE

Insofar as can be judged from the literature the familial incidence of sprue has received very little attention. It is believed that this is the case because the diagnosis has been made in so few instances outside the tropics that there has been little inquiry into its familial incidence. In the family of our second patient, who is a white female, the men seem to have suffered more than the women. However, a sister of the patient who undoubtedly has sprue, has been diagnosed as having "colitis." A brother of the patient has approximately the same type of disturbance as the patient and while the patient's two daughters are perfectly normal her two sons have practically the same type of disturbance as their mother. The fact that the patient's sister and brother remained in Massachusetts while the patient came to Washington at the age of eight and has raised her family here seems to have made little difference in the development of the disease in the members of this family. It is interesting to note also that the son of one of the sisters who is well, has the same type of disturbance as has our patient. Thus from the standpoint of heredity the males and females seem to stand equal chance of transmitting the disease and of contracting it themselves.

SUMMARY

The clinical features by which early sprue as it occurs in temperate climates is recognized, are presented and discussed. It is emphasized that the diagnosis in the early stage is dependent entirely upon subjective sensations. In the absence of any other organic lesion, reliance is placed upon the history of increased frequency of bowel movement, the sensation of abdominal distress, and the exacerbation in in-

testinal peristalsis after ingestion of certain foods. In addition the examination of the stool reveals only soft material or partially undigested foods, but never blood nor pus. A final point in the diagnosis is that of increased mobility of the barium through the intestinal tract so that it reaches the sigmoid at the end of three to four hours after ingestion. Liver extract intramuscularly, repeated at varying intervals, is practically specific treatment.

A case is reported in which sprue is present in a large proportion of the members of that patient's

family. This is believed to be the first evidence of familial incidence of the disease in temperate regions. Both males and females alike seem susceptible to the disease, but it seems that the disease may be transmitted to her offspring by a female who remains well.

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An Unusual Case of Chronic Duodenal Ulcer

By

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CASES of chronic duodenal ulcer have been reported so frequently, at medical societies and in medical journals, that repetition has become boring. Nevertheless the following patient presents such a typical account as regards chronicity, periodicity, rhythmic sequence of events and character of symptoms, such an exceptional variety of possible complications and such a complete picture of the methods of treatment commonly employed, both medical and surgical, that his story seems worthy of special report. Furthermore it raises once more an old question as to whether duodenal ulcer in some instances is ever cured by any plan of management, to the extent that the patient can be assured his symptoms will never recur.

I. *History:* Mr. W. H. M., aged 47, first seen by the writer in August, 1937, began to have trouble with his stomach during the Winter of 1913-1914. He saw no doctor at that time but learned to obtain relief by taking soda. In July, 1914, he had for the first time a severe hemorrhage and vomited large quantities of blood; but recovered after a month of rest in bed. He was better for a while after that but during the Winter of 1914-1915 he had again more or less constant pain in his stomach, although he still sought no professional advice.

In the latter part of April, 1915, however, there occurred a sudden severe attack of abdominal pain, diagnosed as appendicitis by the physician who was summoned in the emergency. He was taken at once to a hospital; and when hot applications to the abdomen all during one night gave no relief, the abdomen finally was opened next morning to remove an inflamed appendix. Much to the operator's surprise, however, he found instead a perforated duodenal ulcer. This was repaired, a gastro-enterostomy was done, and the patient recovered after a lengthy convalescence. But after he returned home more or less constant distress from "gas pains" reappeared and persisted again during the Winter of 1915-1916.

In the Spring of 1916 he consulted a number of different doctors, some of whom advised further surgery, some medical treatment. He finally accepted medical advice, and adopted a routine plan of treatment by diet and alkalis. On this he improved and

continued to feel so much better during the Summer of 1916 and the Winter of 1916-1917, if only he watched his diet, that in April, 1917, he enlisted in the army. He was never sent abroad but in camp in this country, he felt fairly well so long as he could get the character of food required.

In February, 1918, because of recurrence of his stomach trouble, he was sent to the Letterman General Hospital from the School of Aeronautics in Berkeley. The army doctors at the hospital advised immediate operation; and because he declined he was discharged from the Service in April, 1918.

From the latter date until November, 1920, he was continually distressed but able to attend to his work as an automobile salesman, if he observed his diet and took his alkaline powders as prescribed. Then finally he became so much worse that at that time he went back to the Letterman Hospital and submitted to operation as advised. He was told afterward that the gastro-enterostomy was not functioning properly and that below it a lateral intestinal anastomosis had been done. After the operation his condition was variable, with periods of complete comfort and then for no reason at all a recurrence of all symptoms.

In August, 1921, he went to the Mayo Clinic and came under the service of Dr. George B. Eusterman. There he was put to bed for a month and given a routine Sippy course of treatment by milk and cream and powders; but in spite of that, as soon as he got up and moved about, his pains recurred. He left the Mayo Clinic about December 1, 1921, and returned to his home on this Coast.

Nevertheless he was distinctly better after that experience and continued very active for some time so far as business was concerned. But his trouble recurred from time to time in spite of milk and cream diet until finally in May, 1924, because his suffering had again become so intense, he returned to the Mayo Clinic. There in May, 1924, another operation was done by Dr. Will Mayo and Dr. Donald C. Balfour. He was told that the gastro-enterostomy was taken down and the normal continuity restored, by which food was sent through the pylorus and the duodenum. After that operation his condition was much improved, he

had no pains, food tasted good and he felt better than for years previous. He returned home and went back to work.

Then, just sixty days after his operation in May, in August, 1924, his duodenal ulcer perforated again, without warning. He was taken at once to a hospital in San Francisco, the perforation closed and the gastro-enterostomy restored. After this operation comparative peace prevailed for over ten years. He managed to get along with a fair degree of comfort by careful diet and taking complete rest whenever his pains became very acute.

But once more in February, 1936, his condition again became so intolerable that he entered the Veteran's Hospital at Fort Miley, in the effort to obtain relief. This time a new plan of treatment was advised and he was given a series of injections of Larostidin, thirty-six in all. These caused such improvement and such relief from pain that he was discharged cured in April, 1936.

Unfortunately the cure did not last long and in two weeks he was suffering as much as ever. After trying to get along at home for another two weeks, he returned to Fort Miley Hospital four weeks after his first dismissal. Here another series of injections of Larostidin was given, 24 in all this time, with again complete subjective relief. He was discharged the second time in May, 1936, but advised to continue his "shots" at home. In spite of them, however, his pains recurred more or less constantly after he left the hospital the second time. So in February, 1937, he went back to the hospital for another series of injections of Larostidin. He does not know how many he had altogether during his visits there and at home but knows there were over 100. He was discharged the third time in April, 1937, as usual, much better after his rest and injections.

But in spite of all that had preceded, he had another severe hemorrhage on May 31, 1937, and had to be taken back to the Fort Miley Hospital in an ambulance. After routine treatment by ice-packs, discontinuance of food, etc., the bleeding stopped. Ultimately he was placed again on the Sippy diet and alkaline powders and recovered to such an extent that he could be dismissed in June, 1937. The surgeons at this last admission refused to do any further operating.

The above story was obtained from the patient on his first visit to the writer in August, 1937. Although he was then restricting his food to the usual non-residue diet which he had learned by long experience and was taking Upjohn's Nutrochloric tablets regularly, he had much pain not completely relieved by either. He suffered particularly at night, never slept over two hours at a time and when roused by pain he had to take milk or several tablets to get relief.

II. *Physical Examination* showed nothing abnormal except the numerous operative scars in the abdominal wall. The patient's weight was 172 lbs., and the tendency was to gain because of the large amount of milk and cream constantly consumed to relieve pain. The heart was normal in rate, rhythm and sounds and the blood pressure 120 systolic and 70 diastolic.

III. *Laboratory Findings:* There was a moderate secondary anaemia, with hemoglobin 65 per cent and red cells 4,000,000. The Wassermann reaction was negative. The stool showed no occult blood. The urine was cloudy and turbid, alkaline in reaction, with a heavy sediment of phosphates.

Stomach contents removed at 9 a. m., with the patient fasting since midnight in spite of pain, were 60 cc. in amount, with no blood gross or occult, but with total acidity 65 and free HCl 40. After an alcoholic test meal the total acidity in fifteen minutes extractions ran 18, 42, 44, and 50; and the free HCl 8, 26, 28, 34. This analysis is unusual if a gastro-enterostomy is functioning properly, for then regurgitation usually produces an achlorhydria.

IV. *X-ray Films* of the stomach and bowel revealed some interesting details. The stomach filled readily in spite of slight spasm at the cardia. As soon as it had partially filled the cavity, the barium ran through the gastro-enterostomy opening into both sides of the loop of small bowel; but some of it passed also through the pylorus and duodenal cap, both of which were obviously deformed. When the other loops of small bowel were well filled, there was a definite puddle formed in the dilated loop to the left of the stoma, and some fixation was observed at this level, probably due to obstruction by post-operative adhesions below this dilated loop. At six hours the stomach was empty, all the dilated loops of small bowel were likewise empty and the barium had reached the hepatic flexure.

A second barium meal was given twenty-four hours after the first. This showed the stomach completely filled before the gastro-enterostomy began to function. Confirmation was obtained that food passed also through the deformed pyloric end of the stomach and the duodenal cap.

Several suggestive facts were thus brought out by this X-ray examination: (1) There was definite evidence furnished of an old chronic duodenal ulcer with deformity. (2) In spite of previous perforations and operations for repair, the pyloric orifice and duodenal cap were not obstructed but permitted some of the barium at least to leave the stomach by this route. (3) There was spasm at times at the gastro-enterostomy orifice that delayed the exit of stomach contents through it; explaining the presence of hyper-acid secretion in the fasting contents and the failure of regurgitated duodenal contents to keep the stomach neutral. (4) The presence of slight obstruction about five inches beyond the gastro-enterostomy opening with laking of the barium at that point in the loop, might be due to post-operative adhesions or to the lateral anastomosis that the patient said was performed at the Letterman Hospital in November, 1920; but this did not cause a six hour delay.

TREATMENT

By regulation of the kinds of food to be taken, and the hours at which it was taken; by decreasing the number of nutrochloric tablets at night; by allowing instead a minimum amount of a powder containing soda, magnesia and bismuth; and by giving a few drops of the tincture of belladonna three times a day, the patient was afforded relief from pain and comparative comfort, his urine became clear and neutral or slightly acid and he obtained more hours of sleep at night than for weeks before. But the chronic duodenal ulcer remains and it is realized that exacerbation of symptoms or another complication may occur sooner or later in spite of treatment, as has happened repeatedly heretofore.

COMMENT

It is recognized that this is an unusual case, that all

the treatment given not only justified but there is no criticism been effected. The

A REVIEW of the ten years from complicated by reported. V operatively and satisfactory. Several other warrant. Mrs. C., age 41, October 22, 1933, bloody stools, dull and strength, tire; past medi. tire. Functional great many. Cardiac and E at night. G.U. periods were. In August, 1936, deal. Her best of examination

HISTORY

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the treatment given throughout its course has been not only justified but intelligently carried out, and that there is no criticism deserved because a cure has not been effected. The events described simply afford

further proof of what has been repeatedly asserted that in certain instances a chronic duodenal ulcer continues to be a menace no matter what plan of treatment is employed in its management.

A Case of Ulcerative Colitis with Unusual Complications

By

H. N. TAUBE, M.D.

A REVIEW of the American Literature of the past ten years fails to reveal a case of ulcerative colitis complicated by acute appendicitis. Such a case is being reported. Moreover, the diagnosis was made preoperatively and surgical treatment instituted with satisfactory improvement in her primary condition. Several other unusual complications that developed warrant attention.

Mrs. C., age 47, an Englishwoman, was first seen on October 29, 1935, with complaints of 1. Diarrhea and bloody stools, duration two years; and 2. Loss of weight and strength, duration six months. Family history negative; past medical history negative; personal history negative. Functional enquiry—Head and Neck—In 1934, a great many ulcers developed on the tongue that disappeared after one month. Respiratory system—negative. Cardiovascular System—patient tires readily, ankle edema at night. G.U. System—negative. Menstrual history—periods were scanty for the past year (1934) and ceased in August, 1935. Patient is unstable and worries a great deal. Her best weight was 104 pounds; her weight at time of examination was 78 pounds.

HISTORY OF PRESENT ILLNESS

The patient states that for years she would move her bowels with the slightest excitement, worry or emotional upset. In July, 1933, she complained of severe pain around the navel after eating blueberry pie. This pain was soon followed by frequent small, mushy, gassy movements, containing no obvious pathological products and were accompanied by cramps. The diarrhea persisted and was not related to food intake.

In the Spring of 1934, bright red blood, mucus and food began to appear in the stools. At this time, the patient was having seven or eight bowel movements daily. From the very beginning, the patient began to lose strength and weight and was becoming paler. In March, 1934, she was seen by a physician and was hospitalized. There a diagnosis of ulcerative colitis was made. This diagnosis was based on a sigmoidoscopic examination and X-ray. She improved after being on a bland diet, colonic irrigations bi-weekly and a transfusion. However, her bowel movements not only increased to twenty to twenty-four daily, but became watery or mushy with much blood and clots in them, and she developed tenesmus. For the past six months, the patient had noticed that her ankles were swollen in the evening and were normal in the morning. This was associated with shortness of breath on exertion. Her memory was becoming poor, and she was mentally slow, and obviously apathetic.

PHYSICAL EXAMINATION

The patient was a white female, looked about 55 years of age, malnourished, pale and stared into space. **Head and Neck**—Eyes negative except for marked pallor of the conjunctiva. Upper and lower plates. Tongue large and atrophic at the edges. Few small glands in the left anterior cervical fossa. **Chest**—thin-walled and atrophied

breasts. No axillary adenopathy. Respiratory system—negative. **Cardiovascular System**—Blood Pressure—134/80. Pulse—80. Heart—essentially negative except for hemic murmurs at all the valve areas. Radials—early arteriosclerosis. Temperature—99.4. **Abdomen**—thin-walled, moves freely, mild tenderness in the right lower quadrant. Liver—palpable one to two fingers. Spleen—not palpable. Bowel was squashy and peristalsis was audible. The descending colon was cord-like and not tender. **Rectal**—marked external hemorrhoids, spastic sphincter and rectum. Rectum—contained no feces but old blood. **Extremities**—negative. Nervous system—essentially negative. **Fluoroscopy of chest**—essentially negative. **Sigmoidoscopic examination**—mucosa was very granular and bled from multiple pin-point ulcers. The bowel wall was very spastic. No polyps were seen.

Provisional diagnosis:

1. Chronic ulcerative colitis
2. External and internal hemorrhoids
3. Secondary Anemia—nutritional
4. Malnutrition

The patient was admitted to the hospital on October 30, 1935; her weight at this time was 78 pounds.

Laboratory findings—Urine—Specific gravity 1018; Albumen +; Sugar negative; Microscopic negative. Hemoglobin (Sahli) 48% or 6.8 gms. Red blood count 3,900,000; White blood count 6,250; differential normal. Stools—occult blood four plus. Chemistry—Blood sugar 85 mgms.; N.P.N. 35; Cholesterol 160 mgms.; Van den Bergh 3 units. Serum proteins—Serum albumen 5.2; Serum globulin 2.6; Wasserman negative. Gastric analysis showed hypoaclidity with two hour meal. Serum agglutination against dysentery group was negative. Stool cultures were negative.

Barium enema revealed the following:

The colon filled up with extreme rapidity, taking only a few seconds after the first appearance of the barium in the rectum for it to reach the caecum. The entire colon from the splenic flexure down was almost rigid and showed no evidence of haustra. The colon capacity was very markedly reduced (350 cc.)

Treatment—The patient was put on a low residue, high vitamin diet with viosterol, cod liver oil, iron ammonium citrate 120 grains daily; codeine, morphine; and acroflavine 18000 retention enemas six ounces daily; transfusions of 150 cc. were given every two days.

Progress—Five days after admission to the hospital, the patient ran a fever of 102 degrees. The next morning, November 5, she was nauseated and vomited, although the temperature had returned to normal. The same morning she had five bowel movements. At 6 p. m. she vomited her supper. At that time, her temperature was 98 degrees and her pulse was 80. At 9 p. m. she complained of generalized cramps for the first time. The next morning the patient felt well but at 10 a. m. she vomited her breakfast. Her temperature was 99.2; pulse 80; W.B.C. 9,600; differential revealed 92% polymorphonuclears. On examination, there was found a soft, freely movable abdomen with some

tombress just above the right inguinal ligament. At that time, it was felt that we were dealing with either exacerbation of ulcerative colitis with a perforation or acute appendicitis. At 2 p. m. the temperature was 100.1 degrees; pulse was 78; W.B.C. 9,600; differential remained unchanged. At this time, there was definite rigidity in the right lower quadrant. In spite of her poor general condition and of the known rarity of acute appendicitis in ulcerative colitis, history and physical examination demanded immediate surgical intervention. At operation, an acute suppurative appendicitis was found. The appendix was about two and a half inches long and the size of a small sausage. The pathological report was acute ulcerative appendicitis; chronic appendicitis. The patient made an uneventful recovery, reaching a normal temperature by the fifth day. She was constipated for two days following the operation. A series of small transfusions of 150 cc. and a course of parathormone 7 units b.i.d. and calcium were given. On December 2, the patient was discharged, very much improved and having three or four soft formed bowel movements daily. Hemoglobin (Sahli) 72%; R.B.C. 4,400,000. Her weight was 76 pounds.

The patient remained well for the following five months until April 7, 1936, when following domestic trouble, diarrhea recurred. At the time of her second admission to the hospital, she was having twenty bowel movements daily, her weight being 75 pounds; temperature 99, pulse 90, Hemoglobin 70%, W.B.C. 7,200, R.B.C. 4,460,000. Urine was negative except for a trace of albumen. Stools were four plus occult blood and watery in consistency. Mentally the patient was very depressed. She was put on the same regime and began to improve. By the 16th of April, her weight was 77 pounds and stools decreased to six to eight daily. The patient was skin tested with polyvalent antidyenteric serum and on April 17, she was given 5 cc. of the diluted serum intravenously and on the 19th, 10 cc. Five days later, the patient had a severe serum reaction. Her face and tongue became swollen and a vesicular eruption covered the entire body. After being treated for two days, it disappeared. The severity of the reaction militated against continuation of the serum therapy. The patient remained fairly well until April 28th when her temperature rose to 102.6. Examination at that time was essentially negative; Hemoglobin 64%, W.B.C. 8,200, differential 70% polys. By May 1 her temperature had subsided to normal. No explanation could be found for this fever. On May 2, temperature again rose to 105.8; pulse 94, W.B.C. 8,000. Examination was essentially negative except for a slightly swollen tongue. On May 3, the temperature, after having fallen to 99.4 again rose to 105. The patient now began to complain of a sore mouth, difficulty in speaking and incontinence. The right maxillary gland was enlarged and the floor of the mouth was tender. The tongue was markedly swollen and covered with small ulcers. The temperature fluctuated between 99 and 105. Blood cultures were negative. A continuous intravenous, local hot irrigations and transfusions were started but

despite this, the patient became drowsy, listless and was unable to eat or drink. After May 5, temperature began to subside and the patient to improve. The tongue was still mildly swollen but she was able to take fluids. On May 12, the patient developed a croupy cough, inspiratory difficulty, and retraction of the infracavicular spaces was noticed. There was edema of the true and false cords to such an extent that the airway was almost completely obstructed. A tracheotomy gave the patient immediate relief. Bowel movements, however, were involuntary and there was still some difficulty with feedings. The tracheotomy tube was removed on May 28. On June 4, the left submaxillary gland became swollen and a mass was found on the right side of the trachea from which 20 cc. of pus was aspirated. Smear and culture from this material revealed staphylococcus aureus. The patient became irrational, drowsy and weak. Her temperature was 98.4 and pulse 100. Her position progressively became worse and she died on June 21.

Summary of the autopsy findings—The abdominal wall was extremely thin and there was almost complete absence of subcutaneous fat. The intestinal tract, oesophagus to anus, was removed in toto. The stomach was thin walled and atrophic. A duodenal diverticulum, the size of a thumb, was seen 16.5 centimetres from the pyloric end of the stomach and opposite the site of mesenteric attachment. The mucosa of the duodenum and jejunum was thinner than normal. The ileum for 53 centimetres above the ileocecal junction showed marked evidence of thickening and fibrotic changes. The entire mucosal surface was covered with pin-point ulcerations, giving the bowel a velvety appearance, similar to that seen in the large bowel. The appendix was absent but a senn was found at the caecal caecum. The caecum and the whole of the large bowel were much thicker than normal, particularly the distal 45 centimetres. This area was enormously thickened, apparently scarred and almost completely denuded of mucosa. The rest of the large bowel had a velvety mucosa showing many minute pin-point ulcers.

Histological sections made of various areas of the involved bowel revealed a chronic ulcerative enterocolitis lacking the picture usually observed in amebic dysentery and in no way suggestive of tuberculosis. Nothing of note was found in the rest of the abdominal viscera.

SUMMARY

A case of ulcerative colitis complicated by acute appendicitis has been reported. H. L. Bockus (1) reports two undiagnosed cases of ulcerative colitis complicated by acute perforated appendicitis found at autopsy. It is unlikely that this complication is as rare as one would gather from the literature. More frequent case reports would give one a better statistical insight as to its true occurrence.

REFERENCE

1. Bockus, H. L.: Personal communication.

Editorial

THE PAIN OF ULCER

IN 1912 Cannon and Washburn showed that there is a relationship between the contractions of the ball-balloon stomach and the pangs of hunger. These hunger contractions apparently travel down the stomach much as do the normal waves, but there are

some differences between the two types of activity. The hunger contractions tend to come in groups with fairly quiet intervals in between.

It has not been sufficiently recognized in the past that the recording balloon placed in the stomach serves to bring out and make visible the hunger contractions. When one studies under the roentgenoscope the really

any stomach of a ball shot placed any contractions they can be pictures, and then traces between the Only when a little has been inserted enough to (Gianturco).

After revision the pain of ulcer still remains poor are two main th it is due to conti ulcer, and the o hydrochloric of the evidence.

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That the fact that many persons acid in response to stimuli was secreted a valid reaction should be.

A puzzling pseudo-ulcer the morning it goes quiet patients with eating of a neutralized also in the enterotomy in which little of the stomach.

During an and P that rubbing of an ulcer caused typical was bei a relation e brought relief hydrochloric contraction the the pe Some m Hunger com often have from the co

empty stomach of a cat, with the outlines marked by lead shot placed under the serous coat, one cannot see any contractions or waves. They are so shallow that they can be detected only by taking roentgen motion pictures, and then measuring and plotting the distances between the markers in successive "frames." Only when a little air has been swallowed, or a balloon has been inserted, do the tiny contractions deepen enough to become visible to the unaided eye (Gianturco).

After reviewing the literature on the causation of the pain of ulcer the writer's impression is that much still remains poorly explained and controversial. There are two main theories to explain the distress: one, that it is due to contractions of the muscle overlying the ulcer, and the other that it is due to irritation by the hydrochloric acid of the gastric juice. The greater part of the evidence favors the second theory.

The well attested fact that even ulcer-bearing stomachs are often insensitive to the introduction of acid, the fact that there is no close relation between an increase in the acidity of the stomach and a flare-up of pain, and the fact that in the presence of an ulcer, symptoms commonly come and go, all show that at times the patient or the stomach or the floor of the ulcer must be insensitive, while at other times the sensitiveness must be so great that painful stimuli can go through to the brain. Such temporary increases in irritability probably explain the fact that typical ulcer pain is seen often in persons who have no demonstrable break in the gastric or duodenal mucosa. That patients with ulcer are more sensitive to pain during the periods when their symptoms are troublesome has been shown (Crohn).

That the pain is not always due to acid is shown by the fact that typical hunger distress has been seen in many persons in whom the stomach did not secrete any acid in response to food. The fact that under the maximal stimulus of an injection of histamine a little acid was secreted in some of these cases does not constitute a valid reason for "laughing off" this evidence. It should be faced squarely.

A puzzling fact is that patients with either ulcer or pseudo-ulcer will sometimes lose all of their pain on the morning of the first day of a vacation. Why should it go so quickly? It is hard to explain also why many patients with ulcer obtain perfect relief after the eating of a mouthful or two of food which cannot have neutralized much of the acid in the stomach. Puzzling also is the prompt relief that usually follows a gastro-enterostomy or a hemorrhage, especially in those cases in which little if any change is effected in the acidity of the stomach.

During an operation under local anesthesia, Dragstedt and Palmer made the interesting observation that rubbing, pinching, massaging or pulling on a scar of an ulcer on the anterior wall of the duodenum caused typical and severe pain. Curiously, while the pain was being produced in this way, the injection of a solution of sodium bicarbonate into the duodenum brought relief, and the subsequent injection of dilute hydrochloric acid caused the pain to return. Waves of contraction passing over the pars pylorica did not produce the pain.

Some men have maintained that ulcer pain is due to hunger contractions in the stomach or bowel, but others have failed to show any good correlation between the contractions in the stomach and the pain of

duodenal ulcer. Palmer (1927) found an association between hyperperistalsis and pain during only nineteen of 217 periods of observation: most of the time the pain came without any sign of unusual gastric activity. Against the contraction theory is the fact that the pain of ulcer is usually not rhythmic in character.

Wilson made the curious observation that the pain of duodenal ulcer tends to let up when gastric contents came through the pylorus into the duodenal cap.

Two of the most thought-stimulating and practically helpful articles on the causation of ulcers and pain are those by Langenskiöld (Skandinav. Arch. f. Physiol., 120:537-550, 1913) and Mann and Bollman (J. A. M. A., 99:1576-1582, 1932). They showed in dogs with fistulas that unbuffered dilute hydrochloric acid trickling through stomach and duodenum gradually exhausts the defensive powers of the mucosa, producing first distress, and later pain with reddening, irritation, and finally superficial ulceration. The defensive powers of the mucosa are much greater if food has been digested shortly before the experiment begins. Some of the split-products of food that are absorbed evidently help to protect the mucosa.

These studies explain why the pain of ulcer or pseudo-ulcer is best relieved when food is taken within a few minutes after pain appears. In many cases if the patient waits for an hour or two to secure food the relief obtained is imperfect or transient. Furthermore, when pain reappears some morning after a six months' interval of freedom, if food is taken immediately the patient may avoid going on into an attack lasting a month or more.

Apparently, food helps not only by neutralizing and diluting the acid but by protecting the mucosa. Much injury to an ulcer must be done at night when the acid probably irritates for an hour or more before the pain is severe enough to wake the patient. To avoid this some patients might do well to set the alarm to wake themselves at midnight to take a glass of milk.

The experiments of Langenskiöld and Mann and Bollman suggest that peptone might be a good substance to use in a drip for use at night. Some day surgeons may start such a drip immediately after making a gastro-enterostomy to protect the jejunal mucosa during the first, perhaps most dangerous week, when no food is being given to buffer the gastric acid.

In a number of patients it is certain that there is a relation between hunger pain and constipation, or the presence of gas in the colon. There are reasons for suspecting that some hunger pains felt in the epigastrium are due to difficulties encountered by the terminal segment of ileum in pushing its contents into the colon.

In some persons it may well be that the onset of hunger pain at 11 a. m. or 4 p. m. coincides with the peaks of cycles of increased irritability and activity in the whole digestive tract. Such rhythms have been demonstrated in animals and men.

That the pain of duodenal ulcer is not due to contractions of the overlying muscle is indicated by the fact that in man distention of the duodenum with a balloon is more likely to produce nausea, uneasiness, faintness, dizziness, and chilliness than it is to produce pain (Ivy, Bloomfield and Pollard). These symptoms are not seen commonly in cases of ulcer.

Obviously, several types of stimuli can produce pain

in stomach and duodenum, and the most usual one is probably irritation by the hydrochloric acid of the gastric juice. Always the factor of periodic or occasional increases in the sensitiveness of the stomach

or of the nervous system is an important one, and often it appears to be the decisive one in determining when an ulcer will produce pain.

Walter C. Alvarez, Rochester.

Book Review

Clinical Chemistry in Practical Medicine. By C. P. Stewart, M.Sc., Ph.D. and D. M. Dunlop, B.A., M.D., F.R.C.P.E. Price \$4.00, pp. 372, 38 figures and 15 tables. Second Edition, William Wood & Company, Baltimore, 1937.

THIS book constitutes a manual for laboratory diagnosis. It is not an elaborate text of biochemistry or of clinical diagnosis. Only those tests are given and discussed which are most simple and frequently used

in the clinical laboratory. The selection of tests is commendable and the explanation of the theory on which the tests are based is lucid. The second edition is a definite improvement over the first in that certain important omissions have been remedied. Although it is a very serviceable book, it is probably not as extensive in scope as some workers in this field might desire.

A. C. Ivy, Chicago.

Abstracts

CONNOTATIONS

By

H. J. SIMS, M.D.
DENVER, COLORADO

Servius, in 1615, recorded the first recognized case of total transposition of viscera in man. The writings of Aristotle show that he recognized two instances of transposed viscera in animals. Vehemeyer, in 1897, made the first X-ray observation.

In 1733, Calder described atresia of the duodenum. One hundred forty years later Theremin gave the first exhaustive review of the subject.

The earliest reference to obstetrical paralysis of the peroneal nerve was made by Bianchi in 1867. He stated, "these paralyzes usually follow difficult and prolonged labor, in which the foetus presents by the vertex and has to be extracted with forceps."

Soranus (98-112 A. D.) was the first as far as known to teach podalic version before the death of the child. Pare, in 1550, taught the technique.

That trained midwives were known among the Israelites is to be found in the first chapter of Exodus: "And the King of Egypt spake to the Hebrew midwives, of which the name of one was Shiprath, and the other was Puah." Reference is here made to the use of stools. The use of chairs or stools was an improvement over an outgrowth of sitting on the lap for in the thirtieth chapter of Genesis Rachael says, "and she shall bear upon my knees."

Bard of New York, published in 1808, the first American work on midwifery. Dewes, in 1797, gave private

lectures in obstetrics. In 1825, he published a noteworthy system of midwifery. In 1866, Hodge produced the first illustrated text-book on obstetrics. More than one hundred illustrations from wood-cuts appeared in the publication.

The largest ovarian cyst was reported by Spohn. The tumor was estimated to weigh 328 pounds. Ward, of San Francisco, operated on a patient weighing 309 pounds. She lived less than one hour after removal.

Kondoleon, of Greece, first devised an operation for elephantiasis of the extremities. It was not a curative procedure. There was tendency toward return of the enlargement.

Bard reported before the Chicago Gynecological Society the involuntary passing of a dermoid cyst from the anus at the time of a forcep delivery. The microscopic picture resembled that of a dermoid cyst of the ovary.

Rugae, in 1875, reported eight cases of fracture of the vertebral column following breech delivery.

Reference to adenomyoma of the sigmoid was made by Spencer in 1913: The term endothelioma was coined by Golgi in 1869.

Our knowledge of tuberculous tenosynovitis dates from the observations made by Olaf Acrel of Stockholm, in 1756.

Abraham Colles (1773-1843) Professor of Surgery in Dublin, wrote the original description of that fracture known as "Colles fracture."

Eugene Bouchut (1812-1892) introduced intubation of the larynx for croup.

CONNOTATIONS

By

H. J. SIMS, M.D.
DENVER, COLORADO

Lisfranc most probably was the first to amputate the rectum. He reported nine cases from 1828-1830.

Cardiospasm was first described by Purton in 1821, as idiopathic dilatation of the esophagus. Milulicz popularized the term cardiospas. He insisted that the symptoms were due to spasm of the cardiac sphincter at the lower end of the esophagus.

The space of Retzius was described by Retzius, a Swedish anatomist, in 1856.

Beau, as early as 1849, observed the relationship between gynecomastia and improper development of the sex organs.

Klob, in 1861, gave the first description of a right paraduodenal hernia.

Von Walther, in 1811, attempted to partially excise the scapula for a "spongy swelling." The patient died fourteen days later. In 1825, Mutzer successfully removed a portion of the scapula. Total excision of the scapula was performed by Syme of Edinburg, in 1856.

Burnt sponges were used by ancient Chinese in the treatment of goiter. The value of iodine in the burnt sponges has long been known.

Prolapse of the female urethra was described by Solingen, in 1732.

Phlegmonous gastritis was recognized by Varandalus, in 1620, and again by Barel, in 1656.

The term bezoar in early times was used to describe various types of concretions found in the stomach and in-

testines of animals. According to Persian manuscripts, these concretions were used as remedies during the Middle Ages. Trichobezoar is a term used to describe hair balls, commonly found in animals and occasionally in man. The largest trichobezoar in man was described by Davies. The mass weighed six and one-half pounds.

Von Langendorff and Mommsen, in 1877, described osteitis fibrosa cystica, mentioning shortening of the skeleton and occurrence of localized areas known as "brown cysts."

Early men ate the organs of animals because of their mystical value. They ate the raw pancreas of a sacrificed goat in the belief that the gods would give them luck.

CHAIKOFF, I. L., CONNOR, C. L. AND BISKIND, G. R.

Fatty Infiltration and Cirrhosis of the Liver in Depancreatized Dogs Maintained with Insulin. Amer. Jour. Path., XIV, 1:80-101, Jan., 1938.

It has been shown previously by Chnikoff and associates that depancreatized dogs treated with insulin survive for long periods of time when maintained on a diet adequate in calories, proteins, salts and vitamins, but lacking pancreas. But under such conditions a number of pathological changes occur in the animals; bilateral cataracts, disturbances in the blood lipids, especially a fall in the cholesterol esters, and, of particular note, there is a deposit of large amounts of fat in the liver. When pancreas is added to the diet these changes in the tissues are prevented.

The present study concerns the anatomical changes in the fatty livers as seen at varying intervals of time after pancreatectomy. Fat deposition may occur early and may last for a long time but finally a regression of the fat content in the liver takes place. In two dogs living 4 and 5.5 years respectively the fat content had returned to levels close to normal. In 49 dogs studied the livers showed essentially two types of lesions. The first occurred in association with the early infiltration of the fat, while the second change appeared most characteristically in those livers in which a regression of the fat had taken place. Such livers showed an extensive periportal fibrosis with irregular lobulation indicative of cirrhosis. Thus the depancreatized dog provided a new method for the production of experimental cirrhosis. This occurred as a final stage in response to a fatty infiltration of long standing in the liver. Infection seemed to play no part in the production of the cirrhosis, and there were no instances of obstruction in the extrahepatic bile passages found at autopsy. The fat first appeared, after pancreatectomy, in scattered cells within a lobule and slowly extended

outward from the central vein. This was followed by a progressive hyaline atrophy of the whole lobule. The process was slow and stimulated an evascular fibroblastic proliferation. A few lymphocytes and plasma cells were present. Strands of connective tissue then passed about other peripherally located cells, isolated them, and made the process progressive. The time element in the development of the cirrhosis varied in different dogs. The greatest degree was found in a dog living 2.6 years after pancreatectomy. The earliest signs of fibrosis were found only after 1.5 years had elapsed.

N. W. Jones, Portland.

ROZENDAAL, H. M. AND WASHBURN, RICHARD N.

Gastric Secretion in Cases of Pernicious Anemia. Ann. Int. Med., 11:1834-1837, April, 1938.

Alsted has collected from the literature 32 cases of pernicious anemia in which hydrochloric acid was present in the gastric contents. However, many authors believe that achlorhydria is a constant finding in cases of pernicious anemia. The authors have reviewed the records of 906 consecutive cases from the files of the Mayo Clinic, in which a definite diagnosis of pernicious anemia was made. Achlorhydria was found in all the cases. This finding corresponds with the recent report of Sturgis on 600 cases of pernicious anemia. Hurst has observed four cases of pernicious anemia in which secretion of free hydrochloric acid returned following treatment of the gastritis. Achlorhydria was found in 34 of 36 cases in which analysis of the gastric contents was performed from two to twenty-one years prior to the onset of symptoms of pernicious anemia, while in two cases free hydrochloric acid could be demonstrated 19 and 17 years before symptoms of pernicious anemia developed. In only two cases was a hypochromic anemia found at the time of the original examination. The authors believe that pernicious anemia and simple achlorhydric anemia are separate clinical entities.

Hanes M. Fowler, Fort Wayne.

NIXON, EDWIN A.

Diverticulitis. Northwest Medicine, 37:97-100, April, 1938.

Diverticula and their sequelae are the commonest lesions to be found in the colon. Age and constipation cause these lesions to form through weakened musculature in the anti-mesenteric border of the colon and into the epiploic appendages. Roentgenologic examination by the combined barium enema and air injection offers greater opportunities for studying the numbers and location of the diverticula. Surgical treatment of diverticulitis consists in

individualizing the treatment of the complications.

Hanes M. Fowler, Fort Wayne.

COE, HERBERT E.

Imperforate Anus. Northwest Medicine, 37:97-97, April, 1938.

Methods of treatment for imperforate anus are outlined. Various procedures are described for use depending upon the local conditions found. Where the defect is due to a thin membrane occluding the anal opening and a sphincter is present the perineal approach is very satisfactory. In cases where the blind end of the bowel terminates some distance above the anal dimple a colostomy is advisable either as a temporary or permanent measure depending upon the possibility of later construction of an anal canal.

A case is reported which demonstrates most of the difficulties and complications which can occur during the treatment of this condition.

Hanes M. Fowler, Fort Wayne.

ATKINSON, ARTHUR J. AND IVY, ANDREW C.

Menstrual Edema. J. A. M. A., 106:515-517, Feb. 15, 1936.

Certain therapeutic procedures administered with the object of preventing menstrual edema failed with the exception of the administration of the gonadotropic principle from pregnancy urine, which was slightly effective, and emmenin (collip), which was markedly effective. The blood lipids, which varied considerably, were followed for more than ten months in one patient and were not significantly or strikingly influenced.

Hanes M. Fowler, Fort Wayne.

1938 GRADUATE FORTNIGHT OF THE NEW YORK ACADEMY OF MEDICINE

The Eleventh Annual Graduate Fortnight of The New York Academy of Medicine will be held from October 24 to November 4, 1938.

The subject of this year's Fortnight is DISEASES OF THE BLOOD AND BLOOD-FORMING ORGANS.

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In the coming Fortnight, twenty-three hospitals have accepted the invitation to participate by having prepared afternoon clinics and clinical demonstrations which will be coordinated with the evening meetings. The

evening sessions at the Academy will be addressed by recognized authorities in their special fields, drawn from leading medical centers of the United States.

A comprehensive exhibit of books, pathological and research material, diagnosis, treatment and prevention whenever possible, clinical and laboratory diagnostic methods, X-rays, action of drugs and other therapeutic measures. Demonstrations will be held at regular intervals.

Among the main features to be pre-

sented at the meetings, in the clinics and in the exhibit will be:

Pernicious anemia
Other macrocytic anemias
Idiopathic hypochromic anemias
Other anemias benefited by iron therapy
Anemias of pregnancy
Aplastic and hemolytic anemias
The granulocytopenias
Formation and fate of the blood cells
The reticulo-endothelial system
Diagnostic significance of changes in erythrocytes

Diagnostic significance of changes in leucocytes

Infectious mononucleosis

The leukemias

Hodgkin's disease

Lymphomatoid diseases (other neoplastic diseases of the lymph nodes and bone marrow)

The polycythemias

Diseases of the blood in infancy and childhood

The blood clotting mechanism

The purpuras

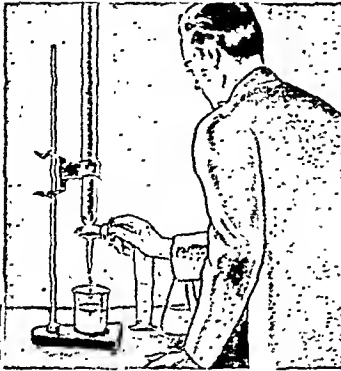
The splenomegalies—their differential diagnosis—indications and results of splenectomy, etc.

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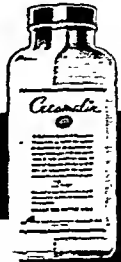
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PALMER, REX B.

Changes in the Liver in Amebic Dysentery With Special Reference to the Origin of Amebic Abscess.
Arch. Path., 24:3-327, March, 1938.

The author comments about the high incidence of liver abscesses in cases of amebic dysentery and the lack of specific information about the mechanism of their origin and development as noted in the literature. Craig collected 1529 cases of amebic dysentery which came to autopsy and found that abscess of the liver occurred in from 22 to 59 per cent in different series with an average of over 40 per cent. Councilman and Laffeur (1921) reported that 21 per cent of 1429 nonfatal cases had recognizable liver abscesses.

It has been believed that amoebae may reach the liver by one of three possible routes: 1. By direct extension through the bowel wall, the peritoneal cavity and the liver capsule. This method is supported by the presence of amoebae in the peritoneal cavity, by the rare occurrence of amebic abscesses of the abdominal wall secondary to amebic dysentery, and by the frequent location of the abscesses near the capsular surface of the right lobe of the liver. 2. By extension through the portal vein. Amoebae are frequently found in lumens of capillaries and venules near the intestinal lesions. 3. By extension through the lymphatics.

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- ⑤ The American Journal of DIGESTIVE DISEASES is not only making friends but it is KEEPING friends. The renewal percentage each year and each month is a positive proof of the sound, month-by-month value of the publication, and it is recognized that this Journal provides today, as no other publication ever provided, a trustworthy postgraduate education in a field much more intricate and fascinating than has been generally supposed.
- ⑤ Once upon a time gastro-enterology was generally regarded as a specialty contaminated by faddism and quackery, but the pioneers, many of whom are still living and active on this editorial board have lifted it to the level of a strictly ethical study—and the Journal is playing an important role in facilitating this important branch of medical practice.

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The Contents Of The July Journal Will Be As Follows:

- A COMPARISON OF STREPTOCOCCI FROM THE COLON WITH BARGEN'S ORGANISM - - - John F. Kessel, Ph.D.
- IV. AN EXPERIMENTAL STUDY OF THE HYDROGEN-ION CONCENTRATION AND CHEMISTRY OF BILE, ITS EFFECT UPON STONES, AND A SUGGESTION AS TO THERAPEUTIC APPLICATION OF OX-BILE IN GALL BLADDER DISEASE - - - Samuel Morrison, Maurice Feldman, John C. Krantz, Jr. and Frances F. Beck
- THE EFFECT OF FEMALE SEX HORMONE "THEELIN" ON GASTRIC ACIDITY - Leon Schiff, M.D. and Henry Felson, M.D.
(With the Technical Assistance of Jane Graff, B.A. and Betty Meyer, M.A.)
- MIGRAINE-EPILEPSY: THEIR ASSOCIATION WITH HYPOTHYROIDISM - - - A. I. Rubenstein, M.D.
- PHENOLPHTHALEIN - - - Horace W. Soper, M.D., F.A.C.P.
- A STUDY OF DISEASES IN THE NEGRO WITH PARTICULAR REFERENCE TO THE GASTRO-INTESTINAL TRACT - - - I. C. Sharon, M.D., M.Sc.(Med.)
- A PRACTICAL METHOD FOR DETERMINING THE CONCENTRATION OF BUFFER SALTS IN THE BODY FLUIDS - - - Anton W. Oelgoetz, M.D.
- TERMINAL ILEITIS-CONSERVATIVE SURGICAL TREATMENT - - - Isidor Kross, M.D., F.A.C.S.
- KARAYA GUM AS A MECHANICAL LAXATIVE. AN EXPERIMENTAL STUDY ON ANIMALS AND MAN - - - A. C. Ivy, Ph.D., M.D. and Bertha L. Isaacs, B.S.
- INTUSSUSCEPTION IN THE ADULT - - - Reuben Finkelstein, M.D., F.A.C.P.

An Open Letter to the Physicians of North America

Do you realize that 60 per cent of all symptoms in general practice arise from the digestive tract?

Many diseases are intrinsic, and many at a distance reflect their symptomatology with great facility in the alimentary canal . . .

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Apparently not. The old rule of thumb—"appendix, ulcer, or gall bladder" is no longer useful. We are becoming gradually acquainted with the disorders and diseases of the colon and reducing this information to some semblance of order. Physiology, bacteriology, chemistry, parasitology, clinical observation, animal experimentation, roentgenology, nutrition, allergy and psychology are the organized methods of approach to a fuller knowledge of

digestive diseases. And there still lies beyond, the dark continent of the small intestine, concerning which so little is positively known.

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This route is doubtful although amoebae have been found in the lymphatics of the colon.

The author reports in detail the gross and histologic changes found in the liver of one case of amoebic liver abscess coming to autopsy in his own service and in tabular form the important points in 18 additional cases of amoebic dysentery which came to autopsy in the services of the Cook County Hospital, the Alexian Brothers' Hospital and the Evanston Hospital during the years from 1929 to 1936.

In the case studied in detail the liver contained wedge shaped areas which resembled infarcts, and probably were, due to thrombosis of branches of the portal vein. In one instance an amoeba

was found in the thrombus. In these areas were small amoebic abscesses. The shape and distribution of the lesions gave the impression that the infection began in a branch of the portal vein and extended along its subdivisions toward the capsule and spread through the connective tissue of the triads into the parenchyma of the liver. It seemed probable that such an infarction due to intrahepatic portal thrombosis was an important factor in the production of the large amoebic abscess.

The periportal connective tissue was increased in 18 of the 19 cases. It was diffuse in some cases, patchy in others. The patchy fibrosis seemed to be healed small abscesses which represented foci in which amoebae had lodged. It seemed

probable that such small scattered abscesses might exist without the formation of large abscesses. The early abscesses begin as areas of lysis extending into the liver parenchyma from the portal triads, without little accompanying inflammatory reaction, and frequently increase in size by coalescing with other abscesses. The central area of liquefaction is bordered by a thin meshwork of fibrinous strands in which there are some lymphocytes and large mononuclear cells. Polymorphonuclear cells are seldom seen. The increase of the portal connective tissue tends to wall off the larger abscesses. This fibrosis also is often present in a diffuse and a focal manner of distribution without abscess formation. With this definite hepatitis there is likewise present degenerative changes in the liver cells—parenchymatous degeneration, fatty changes, hemosiderosis and lysis.

The author concludes that amoebae gain entrance to the liver by way of the portal vein. Abscesses originate in the portal triads.

In only 6 of the 19 cases was a diagnosis of amoebic dysentery made clinically.

N. W. Jones, Portland.

ROBINSON, SAMUEL C.

Exophthalmic Goiter and Gastro-duodenal Ulcer—Two Constitutionally Different Diseases. Illinois Med. Jour., 73:210-223, March, 1938.

Exophthalmic goiter and gastro-duodenal ulcer are shown to be psychogenic diseases yet different in their psyche and soma. The ulcer patient is long and thin. The hyperthyroid may be of any build but tends to be slender and underweight. The temperaments of the two types are contrasting. The goiter patient is fearful, excitable, anxious, juvenile, dependent and frigid, while the ulcer patient is worried, stubborn, inhibited, independent, conscientious, mature and heterosexual.

The two diseases seldom occur in the same individual. The value to be derived from the study of mutually antagonistic diseases is discussed. Pernicious anemia is shown to be a third psychogenic and contrasting disease seldom occurring with either of the other two. A theory of etiology of pernicious anemia is advanced.

Ten males to one female have ulcers while ten females to one male have exophthalmic goiter. The importance of sex predominance in any disease is discussed. The hyperthyroid patient has a rapid pulse, raised blood pressure, increased B.M.R., lowered blood cholesterol values. The ulcer patient has none of these. The goiter patient has lowered HCl values tending toward achlorhydria, enlarged and atonic stomach. The findings in the ulcer patient are the direct opposite. The

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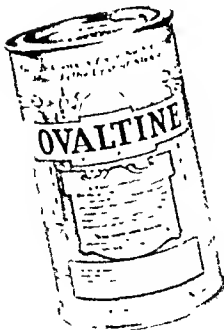
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thyrotoxic patient has a thymico-lymphatic constitution indicative of a juvenile stage of development which is absent in the ulcer patient.

The symptoms, signs and laboratory findings of exophthalmic goiter are practically identical with those produced by overstimulation of the sympathetic division of the autonomic nervous system. The findings of gastro-duodenal ulcer are equivalent to those produced by overstimulation of the parasympathetic nervous system.

Hanes M. Fowler, Fort Wayne.

MEANS, J. H., HERTZ, S. AND LERMAN, J.

Nutritional Factors in Graves' Disease. Ann. Int. Med., Vol. 2, No. 2, pp. 429-437.

It has long been known that marked grades of malnutrition may result from thyrotoxicosis; and this in spite of increased food intake. Lately, however, attention has been called to the fact that malnutrition may cause or precipitate thyrotoxicosis. This was noted by one of the authors, especially in cases following a reduction program for

obesity. A study then by the authors of 35 cases confirmed this observation. In 14, the prethyrotoxic weight loss was occasioned by reduction cures, and the remainder by a variety of conditions such as the restricted diet in the treatment of ulcer, ulcerative colitis and diabetes. Thus may acute malnutrition be added to the better recognized factors which activate thyrotoxicosis.

The authors caution the physician and patient against too vigorous reduction cures for obesity. Also in the preparation of the thyrotoxic patient for operation, they urge that the possibility of nutritional disturbances be considered and if found, an attempt be made to correct them, in addition to the usual iodization.

The manifestation of nutritional disturbances found in the toxic patients, include, as well as general inanition, changes in musculature, skeleton, hematopoietic system, heart and psyche. The methods of correcting these defects include not only a high calorie diet for the general malnutrition but also one high in vitamins and minerals, as well. Vitamin B, in the form of Harris yeast tablets has been of particular value in increasing the appetite and benefiting the heart, in the authors' opinion.

The authors briefly cite several case histories illustrating some of the facts mentioned. In the reviewers' opinion this article is an important and timely one.

B. B. Vincent Lyon,
Nathan M. Noble, Philadelphia.

DOMBROWSKI, EDWARD F., GOLDSTEIN, H. H., BAY, A. P. AND EDLIN, J. V.
Induced Hyperinsulinism. Illinois Med. Jour., 73:147-151, Feb., 1938.

Patients given insulin shock therapy were studied to observe changes produced by induced hypoglycemia. It was noted that symptoms could be grouped under these five divisions: gustatory, vasomotor, neurologic and mental, cardiovascular, and temperature changes.

Gustatory manifestations were among the most frequent noticed, occurred early in the treatment, and consisted of actions indicating a desire for food, protruding and puckering of the mouth, smacking and sucking the lips, sialorrhea, and sucking of fingers, bedding, etc.

Vasomotor phenomena included perspiration and flushing, followed by pallor of the face and body and coldness of the extremities.

Neurologic manifestations noted were chiefly motor in character and included a variety of convulsive seizures, muscle spasms, and evidences of psychomotor restlessness. Hypotonia and diminished reflexes were a rather constant early feature.

The most striking cardiovascular change was an apparent right heart



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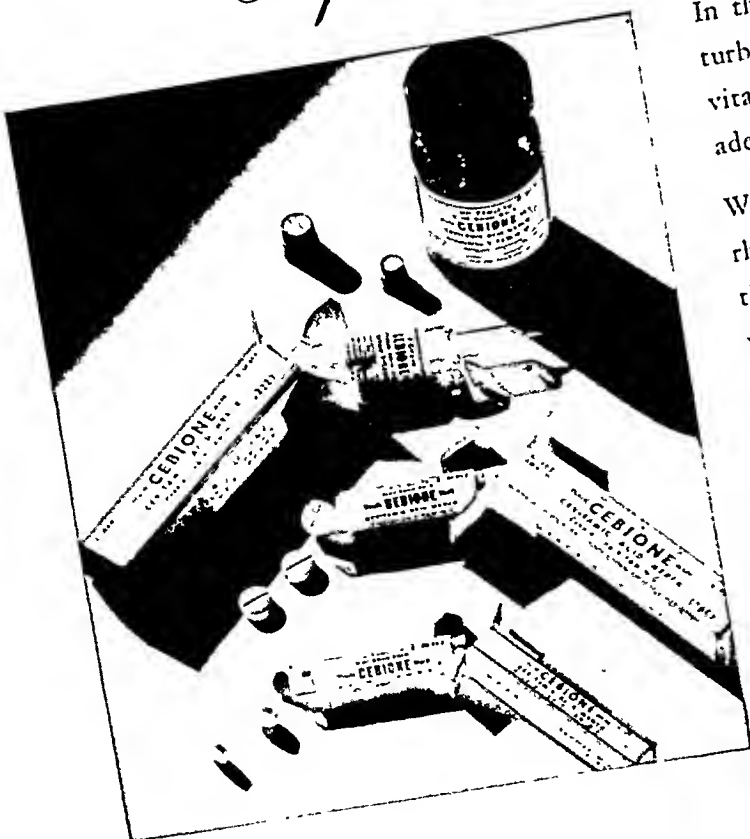
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Cebione is supplied in 0.1 and 1.0 gram ampuls of the crystals for the preparation of solutions for parenteral use and in tablets of 10, 25, and 50 milligrams for oral administration.

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failure occurring a short time after the administration of glucose to terminate the coma.

All the patients showed some fall in body temperature and some showed marked lowering, even to below the lowest reading on the thermometer in spite of externally applied heat. Several of the cardiovascular collapses were noted at periods of lowest temperature. Temperature usually returned to normal within one to one and a half

hours after termination of the treatment.

The authors intend undertaking a more complete study of the separate groups of symptoms noted above.

Hanes M. Fowler, Fort Wayne, IVY, A. C.

An Outline of Liver Functions and Jaundice. Jour. Michigan State Med. Soc., 37:121-129, Feb., 1938.

Jaundice is a symptom of vital importance only when it is associated with

hepatic insufficiency. The seriousness of jaundice depends upon the extent to which the vital function of the liver is impaired or to the extent to which the cause of the jaundice may in time lead to hepatic insufficiency.

The functions of the liver are outlined as regards storage of food materials, manufacture of food materials and other substances, detoxication, blood volume regulation, excretion, and relation to the glands of internal secretion. Factors of safety and regeneration of liver cells and effects of extirpation of the liver are discussed.

White or lightly pigmented bile is found in cases of obstructed common bile duct or in severe toxic or infectious hepatitis. It is chiefly a secretion of the epithelium of the ducts and its presence there always denotes the presence of hepatic injury.

Jaundice is usually due to a disturbance either before the liver, in the liver, or after the liver. Each condition is discussed in detail.

The differential diagnosis of jaundice is discussed with reference to the various liver function tests such as galactose tolerance, hippuric acid test, bilirubin clearance, and bromsulphthalein clearance.

In obstructive jaundice the cause of death is unknown. It is probably due to hepatic insufficiency. A terminal renal insufficiency occurs. Physiologic disturbances seen are osteoporosis, hemorrhagic tendency, bradycardia and pruritis.

"Liver death" and "hepato-renal syndrome" are discussed with theories advanced as to causative mechanism.

In every biliary tract disease the factor of safety in the liver is impaired to a greater or lesser extent. Hence, much attention should be given to the proper preparation of the patient for operation and to the selection of the anesthetic.

The medical aspect of the treatment of jaundice is that for the treatment of hepatic insufficiency, namely, improve the detoxicatory and other functions of the liver. The following measures have been found useful, administration of glucose, calcium, and vitamins, blood transfusion, proper diet including glycine and chondroitin, and administration of bile salts.

Hanes M. Fowler, Fort Wayne.

FOWLER, W. M. AND BARER, ADELAIDE P.
The Etiology and Treatment of Idiopathic Hypochromic Anemia. From the Department of Internal Medicine, State University of Iowa Medical School, Iowa City, Iowa. Am. Jour. Med. Sciences, p. 625, Nov., 1937.

This disease syndrome is seen most frequently in middle-aged women; it is usually associated with deficient gastric secretion, a marked secondary type of anemia with the red blood cells pale



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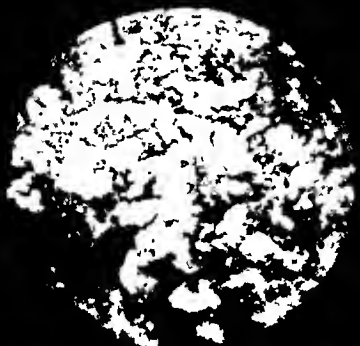
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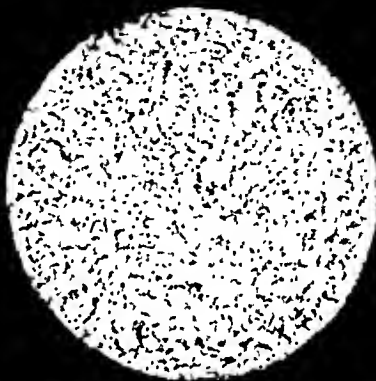
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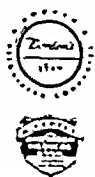
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*Ann. Int. Med. Vol. 9, No. 2, Feb. 1936

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Mead's Brewers Yeast Powder in 6 oz. bottles.

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and small. In typical cases there is dysphagia, glossitis and atrophy of the tongue and the authors say they have never encountered these symptoms in chronic hemorrhagic anemia unassociated with deficient gastric secretion. They differentiate between chronic hemorrhagic anemia and this complex by these features: Koilonychia and paresthesias may be present without cord changes. In a case of a male with chronic hemorrhagic anemia they report the finger nails were thin, brittle and spoon-shaped and note that this state of the nails is not confined to cases of idiopathic hypochromic anemia. The writers questioned their patients carefully regarding menstrual blood loss and did not include those with excessive menstruation as instances of idiopathic hypochromic anemia. In discussing achlorhydria, the frequency with which it is associated with the so-called idiopathic hypochromic anemia, is noted and its possible deterring effect upon the absorption of iron is mentioned. Iron balance studies were made which showed that achlorhydria interferes with the absorption of iron. As dietary deficiency has been suggested as a cause of idiopathic hypochromic anemia the authors found a daily iron intake of from 4.14 to 6.74 mg. showed all of five patients studied to be in negative iron balance but when 4 of these subsequently received from 12.27 to 14.19 mg. of iron per day they were in a positive balance. "These results indicate that the requirements are above the figures given by Farrar and Goldhammer, and more nearly agree with Olson and Daum." No case of idiopathic hypochromic anemia was encountered which the authors considered was due to low dietary iron content alone. They think achlorhydria is more important than restriction of dietary iron intake in most cases. The writers state that there is a similarity between the idiopathic anemias associated with menstrual loss and that of pregnancy. "In one the iron is lost through menstruation, in the other through fetal requirements, and in both there is a deficient absorption of iron because of the achlorhydria." Speaking of iron metabolism the writers say: "It has been assumed that faulty metabolism of iron, aside from improper absorption, may be a causative factor in some cases of idiopathic hypochromic anemia. We have found no concrete evidence in the literature to support this hypothesis xxx."

Treatment: Strauss' dosages of commonly used iron preparations: Reduced iron 3 gm., ferrous carbonate 4 gm., iron and ammonium citrates 6 gm., ferrous sulphate 1 gm. A reticulocyte response may be expected and Heath regards a rise of 0.16 gm. of hemoglobin daily as a lower limit of a satisfactory response when the hemoglobin is below 7.8 gm. per 100 cc. of blood. The ad-



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It is made ready for use, simply by the addition of water. These are simply notes of clinical application during many years:

Abscess cavities	Carbuncle	After tooth extraction
Antrum operation	Rectal fistula	Cleansing mastoid
Sinus cases	Diabetic gangrene	Middle ear
Corneal ulcer	After removal of tonsils	Cervicitis

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NEW YORK

ministration of hydrochloric acid did not increase iron retention nor the rapidity of hemoglobin regeneration. Copper and a liver fraction have also been used with the iron. Regarding the use of iron parenterally the authors' conclusions agree with those of Brock who states that "there is never any indication for injections of iron in the treatment of anemia."

Summary:

1. Idiopathic hypochromic anemia, in most cases, is a chronic hemorrhagic anemia due to menstrual blood loss and an improper absorption of iron due to deficient gastric secretion. There is no evidence of faulty iron metabolism.

2. "Simple achlohydric anemia" is therefore a preferable term.

3. Massive doses of iron produce a more rapid hemoglobin response in hypochromic anemia than do smaller amounts, although 1 gm. and 3 gm. of iron and ammonium citrates per day produce a fairly satisfactory increase in some cases even though achlorhydria is present. These amounts lead to a storage of iron in addition to that used in hemoglobin formation.

4. Neither copper nor a liver fraction, when given in addition to the iron, increased the rapidity of hemoglobin production.

5. Iron, administered intramuscularly in a tolerated dose, did not produce a hemoglobin response."

Allen Jones, Buffalo.

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A Teaspoonful Makes A Tumblerful Of "Jelly"

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MATHIS, JOHN A.

Enteritis. Illinois Med. Jour., 73:325-327, April, 1938.

The etiology of chronic enteritis is outlined as follows:

Mechanical: as by irritating foods. Chemical: (a) hematogenous, as by mercury, (b) direct, by drugs and cathartics. Bacterial: (a) specific, as typhoid bacillus, (b) non-specific, as occurs in achylia, duodenitis, etc.

The most valuable symptoms and findings are: colicky pain after meals radiating to the left hypochondrium of relatively short duration and not relieved by alkalies, a feeling of "unquietness" in the abdomen, and an indescribable feeling of nervousness after food which may be accompanied by sweating, hot flashes, vertigo, feelings of extreme weakness, or even fainting. The most important objective symptom is a tender area about half way between the umbilicus and the left costal margin. X-rays reveal a rapid gastric emptying and hyper-peristalsis of the small bowel. The stool examination is of the utmost importance, in fact, the diagnosis is established on the basis of the fecal content.

The treatment is chiefly dietetic and should be based upon the smooth diet as suggested by Alvarez. If constipation is troublesome, milk, Betalactose, or fruit juices may be used. Mineral

IN COMPLAINTS OF FATIGUE

It May Be Lack of Food Energy

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Uniform composition
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Normal children frequently complain of fatigue. Careful study reveals that they do not consume enough food to provide them with necessary energy requirements, half of which are derived from carbohydrate.

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oil may be needed, especially if astringent drugs are prescribed. Treatment must be adhered to for several months after the cessation of all symptoms.

Hanes M. Fowler, Fort Wayne.

PROGRAM

Preventive medicine will be the keynote of the 23rd annual meeting of the American Association of Industrial Physicians and Surgeons which will be held concurrently with the Midwest conference on Occupational Diseases at the Palmer House in Chicago, June 6th, 7th, 8th and 9th, 1938.

Dr. Edward C. Holmblad, 28 E. Jackson Blvd., Chicago, Chairman of the Program Committee, announces the most interesting program in the history of this organization.

Advance programs of the meeting are available to any doctor interested and will be sent without charge to any practicing physician interested in attending this meeting. The sessions will be open to any practicing physician in accordance with the educational program of the Association to spread the propaganda of preventive medicine and absenteeism of employees.

The very constructive work being conducted by the American Association of Industrial Physicians & Surgeons to co-operate with general practitioners and specialists in not permitting the

practice of industrial medicine to interfere with medicine and surgery in general practice is a refreshing thought to everyone in the medical field and this meeting of the Association at the Palmer House should be productive of great good.

For an advance copy of the program or for information on exhibits, address —Mr. A. G. Park, 540 No. Michigan Avenue, Chicago.

BEST, R. R. AND HICHEN, N. F.

Non-operative Management of Remaining Common Duct Stones.
J. A. M. A., 110:1257, April 16, 1938.

During the past few years the authors have been doing delayed cholangiograms on all cases of common duct drainage or biliary fistula. These have revealed the presence of stones or foreign bodies such as blood clots in ducts which were explored by palpation, probing, scopings, irrigation and suction at the time of operation. Therefore, cognizant of the high mortality attending secondary attacks on the biliary tract, they attempted to dislodge these foreign bodies by various non-operative measures.

The following method has been used, and is extended over a three day period.

On the first 1/100 grain of glyceryl trinitrate is placed under the tongue three times; on the second day atropine, grains 1/100 is given orally or hypodermically three times; on the third day the glyceryl trinitrate is repeated. Each morning the patient is given two drachms or more of magnesium sulfate in warm water and one ounce of olive oil or thick cream is given at bedtime. The common duct is irrigated daily through the T tube, catheter or fistula with normal saline. After this, 10 to 30 cc. of warm, sterile olive oil or lipoiodine is placed in the tube and left there if the patient does not complain of pain. Decholin or proeholen, tablets 3 or 4, are also given four times daily. This routine may be repeated as many times as necessary with several days rest between times. The method is usually contraindicated in complete obstruction because of the danger of hastening liver destruction, and it should never be used in those cases in which jaundice is present.

Francis D. Murphy, Milwaukee.

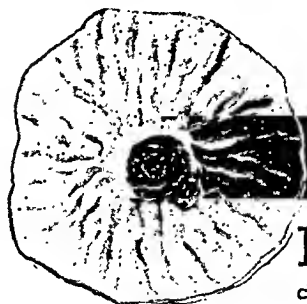
HARTSOCK, CHARLES L.

Differential Diagnosis of Jaundice.
Cleveland Clinic Quarterly, 5:102-107, April, 1938.

By the use of the van den Bergh reaction, jaundice may be separated into two types, namely, hyperbilirubinemia

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IV. SEALING THE TIN CONTAINER

BRIEFLY, the method of food preservation commonly known as "canning" involves subjecting food in a permanently sealed container to a heat process. The heat process destroys spoilage organisms present on the raw food material; the seal on the container prevents reinfection of the food by such organisms. It is, therefore, obvious that the sealing operation—"closing" or "double-seaming" as it is known in the industry—is one of the most important in the canning procedure.

The manufacture of tinplate and "sanitary" cans is described elsewhere (1).

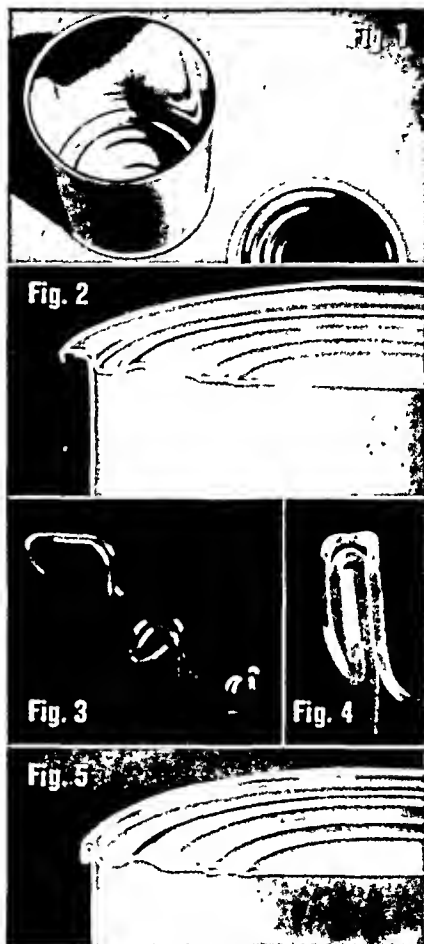
The open cans are received at the cannery in paper cartons or in washed paper-lined box cars, together with the covers which are contained in fiber shipping tubes. Figure 1 shows a can and end ready for use.

In modern canning practice, the cans are first conveyed by automatic runways to can washers, and thence to the filling tables or fillers where the correct amount of properly prepared raw food is put into the cans. The covers or "ends" are placed in the automatic sealing or "closing" machine to which the open can containing the food is mechanically conveyed. In this machine the ends are "double-seamed" onto the can. This operation is portrayed by the accompanying cross-sectional pictures.

In Figure 2 is shown the relation of can to cover before the sealing operation is started; note the relative position of the "curl" on the cover and the "flange" on the can. In this curl, the can manufacturer has placed a gasket or "compound," usually containing rubber. Figure 3 is a series of photographs illustrating the sealing operation in which the curl and flange are first rolled into position and then the layers of metal flattened together to form the final "double-seam" in Figure 4. The rubber compound originally present on the cover supplies the binding material between the layers of metal necessary to insure a permanent or hermetic seal on the container. Figure 5 illustrates in cross-section a closed sanitary can as it comes to the consumer.

In the past twenty-five years great progress has been made in the development of tinplate, compounds and automatic sealing machines. Collectively, these developments enable present-day canners to impose a permanent seal on the cans containing their products more easily and rapidly than ever before in the history of canning.

(1) The Story of the Tin Can, American Can Company, New York, 1935



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This is the thirty-seventh in a series of monthly articles, which will summarize, for your convenience, the conclusions about canned foods which authorities in nutritional research have reached. We want to make this series valuable to you, and so we ask your help. Will you tell us on a post card addressed to the American Can Company, New York, N. Y., what phases of canned foods knowledge are of greatest interest to you? Your suggestions will determine the subject matter of future articles.



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TRI-CALSAATE

due to increased production, and hyperbilirubinemia due to decreased excretion. The first type must be due to some disease that increases the destruction of red blood cells, while the second type must be due to factors affecting the liver or bile ducts, thus interfering with the excretion of the normal production of bilirubin. So-called hematomogenous jaundice, such as is produced by hemolytic blood dyscrasias, hemolytic fevers and certain drugs is easily recognized as such, and the exact cause can usually be determined by appropriate studies.

The real problem in the differential diagnosis of jaundice is presented in those cases due to disease of the biliary system. Three types of biliary tract disease should be differentiated:

1. Cellular damage to the liver. Catarrhal jaundice or Weil's disease, acute yellow atrophy, toxic hepatitis, etc.
2. Diffuse intrahepatic biliary obstruction. The cirrhoses, finely infiltrating malignancies, etc.
3. Extrahepatic obstruction of the large duct. Gall stones, pressure on duct from tumors, etc.

In differentiating between these types of jaundice reliance must be put chiefly upon clinical findings. The galactose tolerance test is one test, however, that yields valuable information if done in cases of early jaundice. This test affords a means of separating off the group due to damaged liver cells in which it is so important that no operation be performed.

Much better diagnostic methods are to be desired to distinguish between the pure obstructive type that is so frequently amenable to surgery and the hepato-obstructive type in which surgery only shortens the patient's lives. At present, however, exploration must be utilized until better methods are discovered.

Hanes M. Fowler, Fort Wayne.

BEST, W. H.

Epidemic Diarrhea of the Newborn. J. A. M. A., 110:1155, April 9, 1938.

This is the study of twenty-seven outbreaks of diarrhea in the newborn which have occurred in the New York City Hospital over the period from July, 1934, to December, 1937. The disease is characterized by the sudden onset of driness in a healthy infant followed within a few hours by loose, watery, yellowish stools containing no mucus or blood. Vomiting and distention may be present. Marked dehydration occurs and death may occur early or late in the disease. It appears to be a disease of infants under four weeks of age and in no instance has it been communicated to adults. It is very contagious and the incubation period usually is short. The outbreaks were

controlled only by closing the maternity service and renovating the nurseries.

The etiologic agent has not been established. Bacteriological examination of the stools has revealed a variety of different organisms in each outbreak. Virus studies also have revealed nothing. The author believes that the cause may be some organism pathogenic for young infants only.

The disease is controlled by isolation, closing of the maternity services until all contacts have been discharged and thorough cleansing of the nurseries. Prevention may be brought about by having everything that comes in contact with the infant's nose or mouth in a surgically aseptic condition.

Francis D. Murphy, Milwaukee.

KESTEL, J. L.

Hypertrophic Pyloric Stenosis in Adults. Jour. Iowa State Med. Soc., 28:147-148, April, 1938.

The author concludes that hypertrophic pyloric stenosis with a moderate degree of obstruction is probably more common than it is generally believed to be. It can be recognized radiologically. Three cases are reported illustrating various degrees of obstruction and retention produced by the pyloric hypertrophy.

Hanes M. Fowler, Fort Wayne.

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The new scientific agent used in the Modern Professional Routine for the physiological treatment of the most prevalent causes of constipation.

Produces normal stools during corrective treatment.

Protocols of laboratory and clinical research and sample upon request.

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CLINICAL NOTES

by KNOX

*(One of a Series of Correspondence Exchanges
with Physicians about Knox Gelatine.)*

QUERY: A doctor writes, "In your literature touching on the use of Glycine (amino-acetic acid) in gelatine for the dystrophies, I suggest that you add Postural or Orthostatic Hypotension for two reasons, first, you will be doing a favor to the medical profession by calling to their attention this disease, and secondly, offering a cheaper manner of obtaining glycine. I am enclosing a letter from a Mrs. — who maintained a systolic blood pressure of 120 when recumbent, but upon standing, it fell so rapidly that she could not get across the room without fainting. All of her symptoms and physical signs were those of Orthostatic Hypotension for which ephedrine hydrochloride had little or no effect, but with the addition of glyceroll, or glycine, 30 grams daily, she has slowly improved and is able to walk for some distance. I would appreciate it if you would send her a menu in which she can get 10 or 15 grams daily of glycine."

ANSWER: Dear Doctor: Thank you indeed for your interesting suggestion. We can add nothing to your noteworthy observation other than to bring it to the attention of the medical profession as widely as possible.

Probably one of the best means of obtaining a concentrated gelatine ration is the following recipe.

"The KNOX FRUIT STIR"

Place the contents of 2 envelopes of Knox Gelatine in an ordinary sauce or cereal dish. Add 8 table-spoonfuls of any desired fresh or canned fruit juice, such as grape juice. Let soak for five minutes and eat with tea-spoon.

Total: 4 ounce mixture—100 calories



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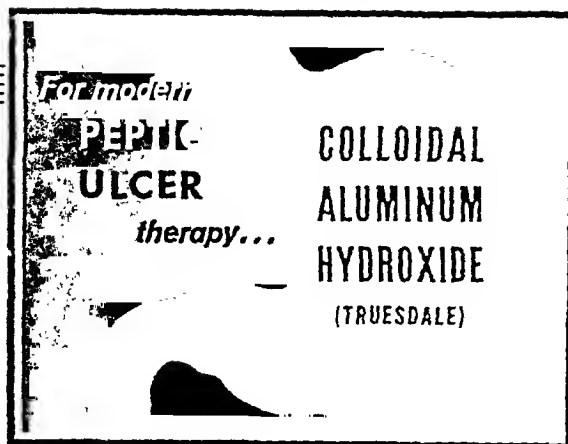
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A Comparison of Streptococci from the Colon with Barger's Organism*

By

JOHN F. KESSEL, Ph.D.

INTRODUCTION

IN the routine culture of fecal material from stools and of scrapings from proctoscopic examinations one encounters numerous Gram positive cocci which have been variously described by different authors as Micrococci, Enterococci, Diplococci or Streptococci. These, for the most part, are diplococci in form and tend to grow in short chains. No marked differences appear between strains, either in morphology, colony formation or action on blood agar plates although attempts have been made by some writers to differentiate them by such criteria.

Eseherich (1886) gave the name *Micrococcus ovalis* to a streptococcus recovered from the stools of children. In 1897 Hirsch and Libman introduced the term

belonging to his alpha type and by fermentation reactions shows sixty-four combinations possible within this alpha type.

Dible (1921) in studying 134 strains of fecal streptococci found that certain of his organisms fermented mannitol while others did not, that they seldom fermented raffinose, and that they were unusually resistant to heat. By his methods they neither produced hemolysis nor formed methemoglobin. He attributes little significance to these organisms as pathogens. He inclines to the view that the term *Enterococcus* should be accepted for the group as a whole since *Streptococcus faecalis*, as described by Andrewes and Horder is limited to mannitol fermenting types and therefore, would exclude many non-mannitol fermenting types.

TABLE I

Fermentation reactions of strains of streptococcus recovered from the colon

Mannitol	Salicin		I	II	III	IV	V	VI	VII	VIII
+	-	<i>Str. faecalis</i>	X	X		X		X		
-	-	<i>Str. mitis</i>	X	X		X				
	-	<i>Str. salicarius</i>	X	X						X
	Raffinose									
	Saccharose									
	Lactose									

Streptococcus enteritis, while in 1899 Thiercelin described in detail a streptococcus from the human stool which he called *Enterococcus*.

Andrewes and Horder (1906) gave the name *Streptococcus faecalis* to a streptococcus from the intestine which they considered occasionally to be pathogenic. The strains with which they worked fermented mannitol, lactose, salicin and sucrose and certain subsequent workers have endeavored to limit the name *Str. faecalis* to those forms from the intestine which ferment these substances.

Besson (1913) accepts the name *Enterococcus* for the common streptococcus of the intestine and considers the same to be a facultative parasite. He is of the opinion that it is widely distributed throughout the body, occurring in the naso-pharyngeal region as well as the alimentary tract. He does not describe its reaction on blood but from the acute condition described as being caused by certain of his organisms it would seem likely that he observed hemolytic streptococci as well as methemoglobin-producing types.

Brown (1919) in his Table 11 lists *Str. faecalis* as

Bagger (1926) isolated ninety-two strains of a streptococcus from cases of peritonitis and fifty-eight strains from the normal intestine. These he designated as *Enterococcus*. His strains all fermented glucose, galactose, maltose, lactose, salicin and mannitol. He differentiated ten types on the basis of biochemic reactions and found them to be pathogenic for rabbits only occasionally. They were somewhat variable in their heat resistance qualities and no mention is made of their reaction on blood. He concluded that agglutination is usually only strain specific and therefore useless for classification.

Barger (1930) and Rankin, Barger and Buie (1932) report a streptococcus isolated from ulcerative colitis lesions which they describe as a diplo-streptococcus. Barger endeavors to differentiate his organism from both *Enterococcus* and *Str. faecalis*, mainly because it does not ferment mannitol, ferments raffinose, is less heat resistant and does not grow well on plain agar. His organism produces methemoglobin on blood agar and by his methods is usually pathogenic for rabbits.

Torrey and Montu (1934) observed the usual differences in heat resistance and in carbohydrate fermentation among their strains isolated from the intestine and conclude that no correlation is apparent

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Submitted November 4, 1937.

between fermentative activity, resistance to heat, other biologic characteristics and serologic relationships.

Since it is apparent that the exact status of *Streptococcus faecalis* and of *Enterococcus* is uncertain and since one in laboratory diagnostic work is often required to pass judgment upon the significance of a streptococcus isolated from the human colon a study was begun in which a comparison was made between a number of strains of such Streptococci, both from normal individuals and from patients who exhibited pathology of the colon in an attempt to determine the biochemic and serologic types present and also to ascertain whether any one type is more closely associated with colitis symptoms than others. With the courtesy of Dr. Bergen it has also been possible to compare several strains of his organism with the streptococci isolated in this study.

METHODS AND OBSERVATIONS

Isolation

In the current study, material procured at proctoscopic examination or from feces, was first planted in carbonated veal infusion broth, pH 7.6, which after 12-18 hours of incubation was streaked on blood agar plates. Colonies were picked from the plates and transferred to mannitol, salicin, lactose, saccharose, raffinose, glucose, aesculin and inulin for strain identification. Most strains were positive in glucose and aesculin and negative in inulin. Therefore these three carbohydrates are not included in Table I. It was usually possible to isolate several different strains of streptococci from each patient by this method and these fall into three different species, *Str. faecalis*, *Str. mitis* and *Str. salivarius*, as classified by Andrewes and Herder, if only mannitol and salicin are considered as differentiating carbohydrates. By the use of three other carbohydrates i.e., lactose, saccharose and raffinose, in which marked variation is shown, each of these

species may be divided into several strains as shown in Table I.

Only ten different fermentative strains as based on the above reactions actually have been recognized to date. Although these ten strains are the same as those most commonly encountered by previous observers they are not thought to be exhaustive and it is probable that additional ones will be encountered.

Fermentation Reactions

Whether this multiplicity of strains is due to their instability of fermentation, or whether there actually are numerous stabilized types of fecal streptococci based on fermentation reactions may still be questioned. Most writers, however, have been inclined to credit their strains with fermentative stability. Among such was Welch (1929), who recognized six different strains.

In the present study relative constancy of fermentation reactions is recognized since eight of the species isolated have been tested frequently in this laboratory over periods varying from one to three years and have remained constant with the exception of one strain of *Str. faecalis*, IV which lost its mannitol fermenting power. A few strains, however, kept for shorter periods of time, illustrated a fermentative variability when first isolated.

It is difficult to compare absolutely the strain relationships of organisms studied by previous workers since identical carbohydrate substances have not been used by all. Brown (1919) in summarizing the work of several previous workers compares the action of alpha streptococci in mannitol, lactose, salicin, raffinose, inulin and saccharose and shows sixty-four possibilities. He suggests a very comprehensive numbering system using units 1 to 8 and decimals 0.1 to 0.8 for the sixty-four strains. *Str. mitis* becomes a1.1, *Str. salivarius* a2.1 and *Str. faecalis* a5.1.

In comparing our ten strains recovered from the

TABLE II
Variation in methemoglobin formation

	Streak Plate Rabbit Blood	Pour Plate Rabbit Blood	Pour Plate Sheep Blood	Blake's Horse Serum Method	
				Rabbit Cells	Sheep Cells
<i>Str. faecalis</i> I	+	+	+	+	+
<i>Str. faecalis</i> II	+	+	+	+	+
<i>Str. faecalis</i> IV	+	+	+	+	+
<i>Str. faecalis</i> VI	+	+	+	+	+
<i>Str. mitis</i> I	+	+	+	+	+
<i>Str. mitis</i> II	+	+	+	+	+
<i>Str. mitis</i> IV	+	+	+	+	+
<i>Str. salivarius</i> I	Not done	+	+	+	+
<i>Str. salivarius</i> II	+	+	+	+	+
<i>Str. salivarius</i> VIII	+	+	+	+	+
Bergen A	+	+	+	+	+
B	+	+	+	+	+
C	+	+	+	+	+
D	+	+	+	+	+
E	+	+	+	+	+

KESSEL—A Co

human intestine with his
serologic relationships are fo

Str. faecalis, I a5.2
II a5.1
IV a5.5
VI a7.1
Str. mitis, I a1.2
II a1.1
IV a2.5
Str. salivarius, I a2.2
II a2.1
VIII a4.5

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III A "Combine
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human intestine with his numbering system, the following relationships are found to exist:

<i>Str. faecalis</i> , I	α5.2
II	α5.1
IV	α5.5
VI	α7.1
<i>Str. mitis</i> , I	α1.2 (Bargen's original organism)
II	α1.1
IV	α2.5
<i>Str. salivarius</i> , I	α2.2
II	α2.1
VIII	α4.5

Of the non-inulin fermenting strains, it will be observed that for the most part, our isolations are identical with the strains most commonly listed in his table. It is, therefore, apparent that certain similar strains of streptococci of the alpha type are recovered most commonly from the human intestine, both by previous observers and in the present study.

Dible (1921) after an exhaustive comparison of 270 strains, divides his organisms into four fermentative groups:

- I A mannitol-fermenting group
- II A raffinose-inulin fermenting group
- III A "Combined" group which splits mannitol as well as raffinose
- IV An undifferentiated group which lacks action on any of these three carbohydrates.

Bagger (1926) working only with mannitol fermenting strains procures ten major groups, most of which have several sub-groups. He uses thirty-two different fermentative substances for comparison. It is obvious that the greater the number of carbohydrates used, the greater will be the number of strains differentiated.

The ten strains found in this study were compared with the following strains of Bargen's organism:

Bargen A	Received from Dr. Bargen in September, 1930.
Bargen B	Received from Dr. P. W. Brown, February, 1933, from an ulcerative colitis patient from whom I had originally isolated the same fermentative species of organism in Los Angeles.
Bargen C	Received from Biologic Firm C
Bargen D	Received from Biologic Firm D.
Bargen E	

Bargen A and Bargen E gave the sugar reactions described by Bargen (1930) as being characteristic of his organism and are identical with Brown's α1.2, and our *Str. mitis*, I. Bargen B, isolated both in this laboratory and in Dr. Bargen's laboratory from the same patient corresponds with our *Str. mitis*, II and to Brown's α1.1. Bargen C corresponds with our *Str. faecalis*, II. Brown's α5.1 and is also identical with the *Str. faecalis* of Andrewes and Worder. Bargen D corresponds with Brown's α5.5 and with our *Str. faecalis*, IV. It is a close variant of our *Str. faecalis*, II differing only in saccharose fermentation.

METHEMOGLOBIN FORMATION

Observers are not agreed in their conclusions concerning the formation of methemoglobin by *Str. faecalis*. Brown (1919) places *Str. faecalis* in the

alpha type and Orcutt (1926) working with the enterococci of calves records the production of green zones on blood agar plates. On the other hand Dible (1921) using Blake's method of testing for methemoglobin reports negative results. Bargen considers that his organism produces methemoglobin. Other writers, for the most part, have neglected statements on this point.

Recent text books also vary in their accounts concerning the reaction of *Str. faecalis* on blood agar plates. Topley and Wilson (1936) state that most strains produce no change in blood agar medium while Zinsser, Bayne-Jones (1934) describe it as belonging to the alpha type. They further state that *Str. faecalis* is probably the same organism which Bargen has associated with ulcerative colitis.

It is a well known fact that the kind of blood used in making tests for the presence of methemoglobin and the type of plate used, whether streak plate or pour plate may be responsible for a variation in results, e.g., a strain of *Str. viridans* will produce a more definite green coloration when sheep blood or horse blood is used than when rabbit blood is used. The appearance on human blood is intermediate between sheep blood and rabbit blood. It is also true that methemoglobin formation is more easily detectable in a pour plate where the colonies are well spaced than in a streak plate.

In this study as shown in Table II a comparison was made between (1) a streak plate and a pour plate, using rabbit blood, (2) pour plates, using rabbit blood and sheep blood and (3) Blake's Horse Serum Method, using both rabbit cells and sheep cells.

It will be seen that the results were somewhat in doubt with certain of the strains when streaked on plates prepared from rabbit blood. In pour plates the methemoglobin formation was more apparent and when sheep cells were used the green coloration was apparent with all strains. With Blake's Horse Serum Method, methemoglobin was formed both in the presence of rabbit cells and sheep cells, though it was de-

TABLE III
Distribution of strains among colitis and non-colitis patients

Strains	Percentage of Occurrence Among Patients with Colitis	Percentage of Occurrence Among Normal Individuals
<i>Str. faecalis</i> I	15	18
II	20	22
IV	15	20
VI	5	5
Total	55	65
<i>Str. mitis</i> I	15	14
II	5	6
IV	15	15
Total	35	35
<i>Str. salivarius</i> I	1	1
II	5	2
VIII	5	1
Total	11	4

tectable in larger amounts when sheep cells were used.

Three representative strains used in this study were sent to Dr. J. H. Brown with the request that he check their methemoglobin production. He kindly did so and in personal communication reports as follows: "In human blood agar all three strains showed slight greenish discoloration about the deep colonies with little or no hemolysis. I regard them as of a weak alpha type although in some media they might appear as gamma type. I have tried to retain the terms alpha, beta and gamma as descriptive terms of appearances in blood agar rather than as names of types of streptococci and I see no objection to describing a streptococcus as producing the alpha appearance in one medium and the gamma appearance in another. In my experience this may be the case with *Str. faecalis* but most strains can be made to produce alpha zones in suitable blood agar."

It is thus observed that the strains of streptococci recovered from the human intestine in this study possess a tendency to produce methemoglobin, although the amount may be somewhat variable, dependent upon the method used for testing. The strains of Bergen's organism observed by comparison also produced methemoglobin but to no greater degree than the strains of fecal streptococci herein described.

DISTRIBUTION OF STRAINS

In this study streptococci have been isolated by culturing smears or scrapings taken by proctoscopic examination from 85 patients showing symptoms clinically designated as ulcerative colitis and from 107 other patients showing no subjective colitis symptoms. The distribution of strains most commonly recovered is shown in Table III. It will thus be seen (1) that the strain representing the original *Streptococcus faecalis* of Andrews and Horder, i.e. our *Str. faecalis* II is the one most frequently recovered both from normal individuals and from patients with colitis, (2) that by the method employed in this study no one strain, even *Str. mitis* I, which corresponds to Bergen's original description is encountered more frequently from patients with colitis than from normal individuals.

Attempts to associate organisms showing lactose or non-lactose fermenting characteristics, mannitol or non-mannitol fermenting characteristics or organisms showing other individual fermentation reactions with a higher percentage of patients exhibiting colitis symptoms than with normal individuals failed.

Heat Resistance

Unusual heat resistance is one of the characteristics of fecal streptococci reported by Dible (1921). He used the ability of streptococci from the intestine as contrasted with other streptococci to survive heating at 60° C. for 30 minutes as a standard. Bergen in 1930 mentions the heat resistance of *Str. faecalis* in contrast to his organism which is less heat resistant.

Rafsky and Manheims (1932) emphasize the heat resistance test as a point of differentiation between Bergen's organism and other fecal streptococci, stating that the *Enterococcus* is viable after heating for one hour at 60° C. while Bergen's strain is killed by such an exposure.

In the thermal death point tests made in this study twenty-four hour broth cultures of the strains to be tested were placed in capillary tubes about four inches

long and the ends sealed. These were placed in a water bath heated to 60° C. One tube was removed in five minutes, one in thirty minutes and one at the end of an hour. There was growth in all tubes removed at the end of five minutes. The results of the thirty and sixty minute tests are shown in Table IV.

It will be observed that of the seventeen individual cultures tested belonging to our ten strains, all with the exception of *Str. faecalis* I resisted the temperature for thirty minutes. Ten of the strains resisted the temperature for one hour. Even certain strains which give the same fermentative reactions as *Str. mitis* and as *Str. salivarius* resisted the 60° C. temperature for thirty minutes. The strains of Bergen's organism tested all survived 60° C. for thirty minutes and three survived a temperature of 60° C. for one hour.

Injection into Rabbits

Although most workers assign a pathogenic role to intestinal streptococci when injected into mice, reports of their pathogenicity in rabbits are variable. Macé (1912) considered them slightly pathogenic, Besson (1913) records intestinal lesions and Bagger (1926) reports moderate pathology. Dible (1921) on the other hand does not consider them pathogenic for rabbits. Bergen (1930 and later) reports intestinal pathology in a relative high percentage of rabbits given intravenous inoculations of his strain of streptococcus.

In this study two rabbits have been inoculated intravenously with each of the various strains of streptococci considered. Two cubic centimeters of a twenty-four hour broth culture from each of the strains here reported and of Bergen A, B, C, D and E were injected into the ear vein of the rabbits. In no case was any diarrhea noted during a period of two weeks and autopsy at the end of that time showed no intestinal lesions to be apparent though necrotic areas were present in the cortex of kidneys inoculated with *Str. faecalis* II and IV, *Str. mitis* I, II and IV and with *Str. salivarius* II and VIII and Bergen A. Culture of these

TABLE IV
Thermal death point tests

	20 Min.	30 Min.	40 Min.	60 Min.
<i>Str. faecalis</i> I	—	—	—	—
<i>Str. faecalis</i> II	÷	÷	÷	—
<i>Str. faecalis</i> IV	÷	÷	÷	÷
<i>Str. faecalis</i> VI	÷	—	—	—
<i>Str. mitis</i> I	÷	÷	÷	—
<i>Str. mitis</i> II	÷	—	÷	÷
<i>Str. mitis</i> IV	÷	—	÷	÷
<i>Str. salivarius</i> I	÷	÷	—	—
<i>Str. salivarius</i> II	÷	÷	÷	÷
<i>Str. salivarius</i> VIII	÷	÷	—	—
Bergen A	÷	—	—	—
B	÷	÷	—	—
C	÷	÷	—	—
D	÷	÷	—	—
E	÷	—	—	—

foci demonstrated in each case the same type of streptococcus that was originally inoculated.

Agglutination Tests

Streptococci from eight of the strains were employed in the agglutination studies as shown in Table V. Antisera were prepared from each strain by intravenous injection first of killed antigen and later of the living antigen into rabbits.

The following observations may be made from a

study of the table: (1) Within certain strains, e.g. *Str. faecalis* II the strain antiserum agglutinated more strains of the same fermentative type (to a titre of 160 or above) than were agglutinated by the antiserum of other strains. (2) This did not obtain for all strains, however, e.g., *Str. mitis* II antigens showed a greater degree of agglutination with the antiserum of both *Str. faecalis* VI and *Str. mitis* I than with antiserum of *Str. mitis* II. One must therefore conclude

TABLE V

Antisera Antigens	Str. Faecalis			Str. Mitis			Str. Salivarius	
	II	IV	VI	I	II	IV	II	VIII
<i>Str. faecalis</i> II	640	80	80	160	160	320	160	80
a.	640	160	160	80	640	320	640	640
b.	640	320	320	160	640	320	640	320
c.	—	—	—	—	—	—	—	—
d.	320	—	160	—	80	40	—	40
e.	320	160	640	40	640	640	160	640
f.	320	40	320	320	640	160	160	160
g.	—	—	—	—	—	—	—	—
h.	—	—	—	—	—	—	—	—
i.	160	160	—	—	80	160	80	—
j.	—	—	—	—	—	—	—	—
k.	—	—	—	—	—	—	—	—
<i>Str. faecalis</i> IV	—	640	—	—	—	—	—	—
a.	—	—	—	—	—	—	—	—
b.	—	640	320	40	160	80	640	—
<i>Str. faecalis</i> VI	320	80	640	80	80	160	—	80
a.	320	320	640	640	320	40	80	80
b.	—	—	—	—	—	—	—	—
c.	80	—	640	—	40	80	—	160
d.	—	—	—	—	—	—	—	—
<i>Str. mitis</i> I	640	320	640	640	640	640	320	640
a.	160	80	40	320	160	40	10	160
b.	160	80	—	160	640	160	160	40
c.	640	320	640	640	640	640	320	640
d.	160	40	—	640	640	320	160	40
e.	—	—	—	—	—	—	—	—
<i>Str. mitis</i> II	320	80	40	320	640	160	640	40
a.	80	—	640	640	—	—	—	—
b.	—	—	—	160	—	—	—	80
c.	80	—	640	640	40	—	—	—
d.	—	—	—	—	—	—	—	—
<i>Str. mitis</i> IV	320	80	160	160	160	640	320	320
a.	—	—	—	—	—	640	640	—
b.	—	—	—	—	—	640	320	—
<i>Str. salivarius</i> II	160	—	—	80	160	—	640	320
a.	—	—	—	80	80	—	160	—
b.	80	80	—	—	160	80	320	160
c.	—	—	—	—	—	—	—	—
d.	160	—	—	80	320	160	640	720
<i>Str. salivarius</i> VIII	—	—	—	—	—	—	—	640
a.	—	—	—	—	—	—	—	—
b.	—	—	—	—	—	—	—	—

that a comparison of fermentation reactions with agglutination tests does not indicate a degree of agglutination within individual fermentative strains that can be considered highly specific. (3) If an attempt is made to group all the strains of *Str. faecalis* together, of *Str. mitis* together and of *Str. salivarius* together it will be seen that the number of positive agglutinations to a titre of 160 or above is greater within each species group than within either of the other two species groups, e.g., there are 25 agglutinations of *Str. faecalis* antigens by *Str. faecalis* antisera while only 18 *Str. faecalis* antigens were agglutinated by *Str. mitis* antisera. Likewise there were 25 agglutinations of *Str. mitis* antigens by *Str. mitis* antisera and only 14 agglutinations of *Str. mitis* antigens by *Str. faecalis* antisera. While these results indicate a slightly closer serologic relationship of the strains within each of the three species here listed it is not as exact as the serologic differences which exist between most species of bacteria and would therefore be of little value in classification.

These results agree in general with those of Bagger (1926) and of Torrey and Montu (1934) who obtained inconsistent serologic results between strains of intestinal streptococci.

DISCUSSION

I. Comparison of Intestinal Types and Upper Alimentary Tract Types.

No satisfactory agreement has ever been reached as to what actually constitutes the intestinal streptococci nor absolute criteria established as to how they may be differentiated from other streptococci. Should all common streptococci recovered from the colon or its contents be regarded as intestinal varieties or should some be considered as throat and pharynx types, that have progressed to the colon? Short chained streptococci from both regions appear to possess similar capacity in the production of methemoglobin. In this study at least all streptococci, which according to the fermentation reactions, might be designated either as *Str. faecalis*, *Str. mitis* or *Str. salivarius*, possess a similar degree of heat resistance.

Gordon (1905) was the first who attempted to differentiate the mouth types from the intestinal types. He compared his series of streptococci recovered from saliva with Houston's series of fecal streptococci. None of his strains found in saliva ferment mannitol and few of them salicin while all the Houston's strains from the feces ferment salicin and certain of them mannitol. A comparison of their most common types with strains recovered in this study will be of interest.

Gordon's second, third and fourth types in order of frequency of occurrence when reduced to fermentative reactions comparable with ours correspond to *Str. salivarius* of Andrewes and Horder, our *Str. salivarius* II. Thomson (1927) in discussing *Str. salivarius* states that many of Gordon's salivary types and of Houston's fecal types are closely related to *Str. salivarius* and that its variants pass by gradations into *Str. faecalis* from which form he is unable to draw any absolute distinction.

It is noteworthy, however, that Gordon's tables show this type (i.e. *Str. salivarius*) and its raffinose fermenting variant, our *Str. salivarius* I, to occur many times more frequently in the saliva than any other type and that these types are rare in Houston's, in Dible's and in our series of intestinal streptococci.

The type occurring next in frequency in Gordon's salivary types possesses the same fermentation reactions as *Str. mitis* I and Bagen A of this study.

Among Houston's strains from the intestine the first two in order of frequency have the same fermentation reactions as *Str. mitis* (Andrewes and Horder), our *Str. mitis* II or Bagen B of this study. *Str. mitis* I or Bagen A just mentioned above is a closely related form varying only in raffinose fermentation. Dible (1921) in his Table I lists 142 strains, fifty of which are either our *Str. mitis* I or II. Thomson (1927) in discussing *Str. mitis* states that this form is essentially saprophytic, occurring chiefly in human saliva or feces.

The variety occurring third in frequency in Houston's intestinal types and most commonly in this study corresponds to *Str. faecalis* (Andrewes and Horder), our *Str. faecalis* II or Bagen C of this study. It is also the most common type recorded in Dible's Table I. This type was not reported in Gordon's salivary series.

Judging from these comparisons one would conclude: (1) The type of streptococcus known as *Str. salivarius* is the form encountered most commonly in the mouth, the same being found less frequently in the intestinal contents. (2) The types known as *Str. mitis* and *Str. faecalis* are encountered more frequently from the intestine.

The question arises as to the justification for regarding these three as separate species and one can not answer this with certainty until a criterion for species differentiation is established for streptococci.

If one could correlate fermentation relationships with agglutination types or with some other serologic identity with as great constancy as one does in certain other groups of bacteria, e.g., the typhoid-dysentery group, the problem would be simple. Since no one type appears to be more pathogenic than another, one must select either fermentation reactions or serologic relationships as an initial basis for comparison. For present comparison, fermentation reactions are emphasized since most workers have selected these in the past and since no evidence has been presented to demonstrate the presence of stable serologic types.

II. Name for Intestinal Types.

Several names for the streptococci from the intestine are encountered in the literature, the three most common being *Streptococcus enteritis* Hirsch and Libman (1897), *Enterococcus* by Thiercelin (1899), and *Streptococcus faecalis* Andrewes and Horder (1906). The original description given to the last species limited the same to mannitol, lactose, salicin and saccharose fermentation types while no similar specific biochemic limitations have been assigned to *Str. enteritis* or to *Enterococcus*. Since the organisms in question are morphologically streptococci, they should all be assigned to the genus *Streptococcus* which has the priority over *Enterococcus*. The word *enterococcus* is nothing more than a descriptive term, indicating the region of the body in which the organisms are commonly encountered and should not be used to designate a genus. The species name *enteritis* would indicate an organism causing an acute inflammatory condition and for this reason does not convey the correct impression of the relationship of the streptococci under discussion. Fortunately the term is not commonly used in recent literature and since the descrip-

tion originally applied to this organism indicates a mixture of α and β types this name should not be retained.

If Brown's suggestions are accepted that the reactions of streptococci in media containing blood are variable and that the terms α , β and γ should be used as descriptive terms only, then *Str. viridans* should not be retained as a species name for this group.

One is left then to consider two main possibilities: (1) Accept the species name *Str. faecalis* and enlarge its definition to include not only mannitol fermenting types but non-mannitol fermenting types of short chained, heat resistant methemoglobin producing streptococci. (2) Accept the three species names *Str. faecalis*, *Str. mitis* and *Str. salivarius* as given by Andrewes and Horder (1906) and differentiate the same in a manner similar to that indicated in Table I, or in Brown's Table II allowing for several fermentative strains within species.

For the time being the second alternative would present the fewest difficulties and is therefore used in this study as a simple method of procedure, each species being further subdivided into strains as shown in Table I. Agglutination studies already summarized also tend somewhat to substantiate this division, although they are not regarded as being actually specific.

Brown (1919) Table II, has already suggested a practical method for divisional grouping of streptococci. His arrangement of the carbohydrates, however, in so far as the alpha strains are concerned seems somewhat unfortunate since one of the first practical divisions of these streptococci would seem to be on the basis of inulin fermentation which would separate the pneumococcic types from the more common streptococcic varieties.

Most intestinal strains fail to ferment inulin and the arrangement of these non-inulin fermenting strains in Table I is suggested as a means of simple grouping. On the basis of mannitol and salicin fermentation it is possible to differentiate the three species *Str. faecalis*, *Str. mitis* and *Str. salivarius*, names already encountered in the literature. On the basis of their additional reactions in lactose, saccharose and raffinose, eight fermentative strains are possible within each species. In practice, all these have not been encountered; the ten strains here recorded being the ones most commonly found in this study and by previous workers. They may, therefore, be expected to be the ones most frequently encountered in the future.

III. Relation of Bargaen's Organism to These Species.

Bargaen (1930) described his organism as follows: "The diplococcus ferments dextrose, lactose, saccharose, maltose, raffinose and salicin, but usually not mannite." Since then he apparently has enlarged the scope of his organism to include other fermentative types which correspond to several of the other fecal types compared in this study. Five of his strains which were compared in this study gave fermentation reactions, one each corresponding with our *Str. faecalis*

II and IV and with *Str. mitis* II and two with *Str. mitis* I, the last being identical with his original description. Five other strains of Bargaen's organism described by Torrey and Montu (1936) fall into two different groups, J. B. being *Str. faecalis* I and L.S., W.M., O.J.T. and H.D. being *Str. salivarius* I.

There would therefore, appear to be no merit in attempting to differentiate the streptococcus which of late has come to be known as Bargaen's organism or the "diplo-streptococcus" of Bargaen from other common streptococci of the intestinal tract.

In this study autogenous antigens prepared from the ten specific strains collected from colitis patients have been used both as antigens for intradermal tests and as bacterins for therapeutic purposes, both in conjunction with and without Bargaen's commercial antisera. Intradermal tests on patients with ulcerative colitis have shown positive reactions with antigens other than the Bargaen A organism just as frequently as they have with antigens prepared from *Str. mitis* I or from Bargaen A organism.

SUMMARY

1. Streptococci isolated from stools and from proctoscopic scrapings of patients exhibiting symptoms of colitis and of individuals with no colitis symptoms have been compared with five strains of streptococci commonly designated as Bargaen's "diplo-streptococcus."

2. The streptococci observed have fallen into ten different fermentative strains when grown in media containing inulin, mannitol, salicin, lactose, saccharose and raffinose, respectively.

3. Representatives of all the strains compared in this study have produced methemoglobin on blood agar plates, have resisted a temperature of 60° C. for thirty minutes, and have exhibited similar morphologic and cultural characteristics. None has produced intestinal lesions when injected intravenously into rabbits, though kidney lesions have been a common result of such injections.

4. By the use of mannitol and salicin only, it is possible to refer each of these ten strains to one of the following species of Andrewes and Horder: *Str. faecalis*, *Str. mitis* or *Str. salivarius*. By the additional use of lactose, saccharose or raffinose, several strains of each species have been recognized.

5. Agglutination reactions do not correlate to any appreciable degree with the ten fermentative strains listed. A closer relationship exists, however, when all strains which give the fermentation reactions of *Str. faecalis*, *Str. mitis* and *Str. salivarius* respectively are grouped together.

6. No one strain has been associated more frequently with ulcerative colitis patients than with non-colitis patients.

7. Of the five strains of Bargaen's organism compared, one was identical with our *Str. faecalis* II which is also identical with *Str. faecalis* of Andrewes and Horder; one with *Str. faecalis* IV which is a variant of *Str. faecalis*; one is identical with *Str. mitis* of

Andrewes and Horder, our *Str. mitis* II; one with our *Str. mitis* IV and two with our *Str. mitis* I. Borgen's strains in our hands did not exhibit any apparent differences from our strains in (1) the action on blood plates, (2) heat resistance qualities or (3) pathogenicity in rabbits.

8. There would, therefore, appear to be no reason

to regard the streptococci described as Borgen's diplo-streptococcus as being essentially different from other types of alpha streptococci commonly recovered from the human alimentary tract and his strains may belong to the species *Streptococcus faecalis*, *Str. mitis* or to *Str. salivarius*.

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IV. An Experimental Study of the Hydrogen-Ion Concentration and Chemistry of Bile, its Effect Upon Stones, and a Suggestion as to Therapeutic Application of Ox-Bile in Gall Bladder Disease*

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THERE are many factors to be considered in the etiology of gall stones. Although much has been written regarding the formation of stones there are but few significant contributions on this subject. It is noteworthy that but little investigative data exist on the hydrogen-ion concentration of bile and many of these have been obtained from fistulous bile in both humans and animals. As to the relation between the hydrogen-ion concentration of bile and the formation of gall stones, the literature is especially scant.

pH DETERMINATIONS IN NORMAL ANIMALS AND MAN

Hydrogen-ion determinations by the electrometric method were made of the gall bladder bile from the guinea pig, dog, rabbit and the human. The pH in a series of 26 normal guinea pigs averaged 8.9. In the normal dog the pH of a series averaged 6.2. The rabbit gall bladder bile was 8.8; cat 5.3 (Okada); ox 7.5 (Okada). The normal human gall bladder bile ranged between 7.0 and 7.5. These findings indicate that the hydrogen-ion concentration of bile varies in different

species and demonstrates that in the herbivorous animal the bile is normally alkaline while in the carnivorous animal the bile is more likely to be acid. On the other hand, in the human subject, an omnivorous species the hydrogen-ion concentration of gall bladder bile is close to the neutral point.

THE EFFECT OF DOG'S BILE ON STONES IN VIVO

In a previous study (1) the authors confirmed the findings of others (2), that gall stones of the cholesterol type placed in the dog's gall bladder would dissolve. Numerous explanations have been advanced to account for this phenomenon, but none seems to be entirely satisfactory. A constant finding in the dog's gall bladder bile is its acidity which possibly may be one of the factors concerned with its capacity to dissolve stones. It occurred to us that since in the dog there was apparently a relationship between the pH of bile and the dissolution of gall stones it would be desirable to select an animal with an alkaline gall bladder bile in order to determine its effect upon similar gall stones. The guinea pig was selected for these experiments. We were able to demonstrate that gall stones placed in the guinea pig's gall bladder were not affected by the

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alkaline bile. Furthermore, it was also noted that no change occurred in the pH of bile owing to the presence of stones.

COMPARATIVE STUDIES OF NORMAL BILE AND FISTULOUS BILE IN RELATION TO THEIR EFFECTS UPON GALL STONES AND HYDROGEN-ION CONCENTRATIONS

As it has been shown that human gall stones will dissolve in normal dog's acidic bile and will not dissolve in the normal alkaline bile of the guinea pig it seemed important to determine what effect a dog's alkaline bile would have on the dissolution of human stones.

In a previous communication (3) we have shown that the normal dog's acidic bile could be made alkaline by the production of a fistula which prevents concentration of the bile by the gall bladder. These studies demonstrated that when gall stones were implanted into the gall bladder through the fistulous opening, the dissolving effect of the bile was lessened, and in fact in some instances there was actually an increase in weight of the stones. These observations seem to indicate that alkaline bile may have some tendency to favor the formation of stones but this has not as yet been definitely proved.

It is interesting in this connection to point out that Neilson and Meyer (4) observed that in gall bladders of various laboratory animals injured by infection the pH of the bile remains constantly identical with that of the secretion derived from the liver owing to the inability of the gall bladder to bring about its usual change in the bile.

EFFORTS TO CHANGE THE pH OF BILE BY FEEDING OF VARIOUS SUBSTANCES

(a). CHEMICALS

Gall bladder bile possesses a high buffer capacity and it is difficult to alter its hydrogen-ion concentration. This applies also to the concentrations of its various constituents. The feeding of various chemical

substances to animals has little tendency to change the hydrogen-ion concentration of gall bladder bile. Even drugs known to be excreted partially by the liver such as salicylic acid showed no influence upon the pH of gall bladder bile. Ottenheimer and Kahn (5) found that the oral administration of sodium citrate, sodium bicarbonate or hydrochloric acid failed to cause any significant alteration in the pH of bile. They also noted that solutions of phenoltetrachlorophthalein and phenoltetraiodophthalein when injected intravenously in animals seemed to be excreted in a colloidal state and have no effect on the reaction of bile.

(b). FOODS

Since the chemicals employed had little effect upon the pH of bile it occurred to us that feeding experiments might change the pH. Three normal dogs were placed upon a vegetable diet consisting of lettuce, carrots, cabbage, etc. After a period of 18 days the bile was obtained directly from the gall bladder and hydrogen-ion determinations made. The following pH values were obtained in the three animals—6.92, 6.29 and 6.26—which indicates that the feeding of vegetable diet to dogs had no significant effect on the pH of the bile. In another experiment four guinea pigs were fed a meat diet in order to determine whether their alkaline bile could be made acidic by this change of diet. After a feeding period of 14 days the following pH determinations were obtained—8.74, 8.63, 8.86, 8.64. These are essentially normal values for the guinea pig, and thus it is readily seen that the change from a herbivorous to a carnivorous diet produces no significant change in the pH of bile in these normal animals.

Bronner (6) in 1933 studied cholecystectomized human subjects with a tube in the ductus choledochus and observed that by varying the diet he was able to shift the pH of the bile to the alkaline side with a vegetable diet and to the acid side with a meat diet. Bronner believes that variations in the pH and changes that occur concomitant with it are important factors

TABLE I

Effect of powdered ox-bile U.S.P. on bile pH and stone weight in dogs. Eight grams daily by mouth

Dog	Before Implantation of Stone		After Implantation of Stone		Total No. Days Fed	Weight of Stone in Grams		Weight Loss in Stone Grams	Weight Loss in Stone Per Cent
	pH	Days Fed	pH	Days Fed		Implanted	Recovered		
1	8.04	18	8.76	90	108	1.076	0.046	1.030	95
2	6.44	18	8.50	90	108	3.318	0.069	3.249	98
3	8.70	18	8.54	90	108	0.998	0.879	0.119	12
4	6.23	7	8.06	27	34	0.937	0.226	0.711	74
5	6.65	7	7.55	39	46	1.428	0.240	1.188	83
6	8.46	7	7.52	39	46	0.504	0.112	0.392	77
7	8.24	7	None	30	37	1.054	1.000	0.054 (Abscess G.B.)	7.7
8	7.5	11	None	67	78	1.037	0.112	0.925	89
9	8.02	11	8.27	67	78	0.914	None	No stone found	
10	8.18	11	None	68	79	1.190	0.328	0.862	72
11	6.32	21	6.12	60	81	0.731	None	No stone found	
12	7.10	14	None						
13	7.10	17	7.47	40	57	0.893	0.282	0.611	68
14	6.65	17	6.48	42	59	1.818	0.105	1.713	94

in the origin of stones. Notwithstanding Bronner's observations on the effect of food upon fistulous bile in the human subject it is our opinion that these changes actually occur in liver bile and not in normal gall

The pH of this bile was determined immediately with a glass electrode. Following ox-bile feedings the pH values approximate those of liver bile. The results are recorded in Table I.

TABLE II

Effect of ox-bile on bile pH and stone weight in dogs. 0.6 grams daily by mouth

Dog	Before Implantation of Stone	After Implantation of Stone	Total Days Fed	Weight of Stone in Grams		Weight Loss Grams	Weight Loss %
	pH	pH		Implanted	Recovered		
1	6.48	None	42	0.793	None		
2	None	6.07	77				
3	None	6.89	82				
4	7.75	6.61	62	1.713	0.692	1.621	95
5	6.68	6.41	82	1.952	1.600	0.352 (calc.)	18
6	6.68	6.21	77	1.135	0.443	0.695	61

bladder bile. Our experience, at least in the normal dog and guinea pig, does not confirm Bronner's findings in the fistulous human subject.

(c). VITAMINS

In a previous communication (1) we reported, as the result of our experiments, that the feeding of vitamins A, B-complex and D had no significant effect upon the formation or dissolution of gall stones in the dog.

(d). OX-BILE

Since few drugs are known to effect the hydrogen-ion concentration of bile we decided to use powdered Extract Ox-Bile, U. S. P. as an oral medication. Fourteen dogs were utilized in this experiment. Two tablespoonfuls (8 grams) of ox-bile were mixed with the dog's rations and fed over a period of weeks. Interesting results were obtained from these experiments. It was found, for instance, by feeding large amounts of ox-bile that the dog's normally acidic bile could be changed to alkaline. No untoward effects developed from this dosage of bile.

Following the oral administration of ox-bile it was observed that the gall bladders were considerably distended. The bile was obtained aseptically by hypodermic needle puncture. Its color was altered from the normal dark brown to a striking deep olive green.

THE EFFECT OF FEEDING OX-BILE AFTER IMPLANTATION OF GALL STONES INTO THE GALL BLADDER

In 14 animals which had previously been fed daily with 8 grams of ox-bile, a cholesterol gall stone was placed in each gall bladder to determine the effect of this alkaline gall bladder bile upon the stones. After a varying period of time (see Table I) it was observed that a marked diminution in the size of the gall stones took place. It seemed therefore that the hydrogen-ion concentration of the bile was not the sole factor in the dissolution of gall stones as was suggested in our previous investigations (3, 7). However, chemical analysis of these biles resulting from the feeding of ox-bile disclosed a decrease in bile acids and a diminution of protein. The diminished amount of protein resulting from dilution binding less of the normally occurring cations of bile, may account in part for the alkalinity.

THE EFFECT OF FEEDING SMALL AMOUNTS OF OX-BILE

Inasmuch as large doses of ox-bile changed the pH of dog's acidic bile to alkaline it was of interest to determine whether a similar response followed small doses, approximating the normal human dosage. Six dogs were observed in this experiment. Two, ten grain capsules of ox-bile daily were administered orally to each dog. It is noteworthy that in these experiments the pH of the dog's gall bladder bile did not change

TABLE III

Effect of Keto bile acid on bile pH and stone weight in dogs. 0.7 grams daily by mouth

Dog	Before Implantation of Stone		After Implantation of Stone		Total Days Fed	Weight of Stone Implanted	Weight of Stone Recovered	Weight Loss Grams	Weight Loss %
	pH	Days Fed	pH	Days Fed					
1	7.61	28	6.11	37	65	1.410	0.674	0.756	54
2	6.62	47	6.17	38	81	1.244	0.752	0.462	36
3	6.62	27	7.21	37	65	1.028	0.507	0.591	58
4	7.61	27	6.17	37	65	1.612	0.493	0.579	36
5	6.75	28	7.30	37	65	1.252	0.746	0.666	53

following the administration of such small doses. These experiments would indicate that to obtain results in gall bladder disease larger doses would be required in order to influence the composition of bile and thereby probably obtain better therapeutic results (see Table II).

CHEMICAL STUDIES

Chemical studies have been made of the gall bladder bile following the feeding of bile salts. Our results are summarized in Table IV. It is interesting to note in studying this table that the effect of feeding large

TABLE IV
Summary of averages in bile studies

No. of Dogs*	Treatment	pH	Total Solid Grams %	Mucin Grams %	Ash Grams %	Alkalinity %	Lipoids Grams %	Bile Acids %
8	Normal	6.17	22.77	1.29	2.04	0.78	6.51	6.78
19	Ox-bile**	7.68	17.84	0.75	1.72	0.57	4.78	5.0
8	Ox-bile*** Average	6.66	21.67	1.67	0.69	6.37	6.09	6.59
9	Keto bile acids**** Average	6.59	19.19	0.87	1.79	0.62	5.16	5.36

*Refers to a larger series than is recorded in the other tables.

**8 grams daily.

***0.6 gram daily.

****0.7 gram daily.

THE EFFECT OF FEEDING MIXED KETO BILE ACIDS

Five dogs were observed in this experiment. To each animal 3, 3 $\frac{3}{4}$ grain tablets* were administered daily by mouth. The results indicate that on the whole the feeding of keto acids in small dosage did not materially change the pH of bile. It would seem at least from these few experiments, that the dissolution of stones was less than was found in the control or after the feeding of ox-bile. (see Table III).

TABLE V
pH of human bile

Case	Ailment	pH
1	Gall Stones	8.65
2	"	8.04
3	"	8.26
4	"	8.60
5	"	7.44
6	"	8.70
7	"	8.46
8	"	8.64
9	"	8.02
10	"	8.05
11	"	7.90
12	"	7.2
13	"	7.71
14	"	7.55
15	Cholecystitis	7.4
16	"	7.63
17	Pancreatic Cancer	7.31
18	"	7.60
19	Pancreatitis	7.18

doses of ox-bile is to dilute the various constituents of the normal dog's bile. This is associated with an increase in the pH. On the other hand, small doses of ox-bile have been found to be ineffective in changing the chemical proportions of the various constituents nor do they change the hydrogen-ion concentration. These experiments suggest that feeding of ox-bile in small doses as is ordinarily administered in the human subject, is therapeutically ineffectual.

Following the feeding of keto bile acids it is of interest to note that although there was considerable dilution of the chemical constituents of the bile the pH was not significantly altered. By comparing the effect of ox-bile with keto bile acids it is readily observed that the ox-bile in large quantity appears to have a greater diluting effect.

HUMAN BILE

As the result of our studies on animals, we became interested in the hydrogen-ion concentration of gall bladder bile in human cases of pathological and normal gall bladders. Biles were obtained at operation from gall stone cases and hydrogen-ion concentrations were determined on the fresh bile. Strikingly enough, it was noted that in each case of gall stones which we examined, the hydrogen-ion concentration of the bile proved to be alkaline. These studies corroborate the data already obtained in our animal experimentation. In 15 human subjects possessing gall stones the hydrogen-ion concentration determinations obtained are higher than normal. (See Table V). We have also found that the type of stone did not significantly influence the pH in these human cases. The results of other pathological conditions are also recorded in this Table.

CONCLUSIONS

1. In a study of gall bladder bile of different species one of the most striking features is the apparent immutability of its characteristic hydrogen-ion concentration.

2. The pH of bile does not readily change following various forms of therapy.

3. It is our belief that various foods do not significantly alter the pH of gall bladder bile.

*This material was kindly supplied to us by G. D. Searle & Co., Chicago, Illinois.

4. The feeding of large doses of powdered extract ox-bile U. S. P. changes the dog's normal acidic bile to alkaline and also dilutes the chemical constituents. Feeding of smaller doses does not change the pH of gall bladder bile in the dog nor does it have any diluting effect.

5. The feeding of keto bile acids (0.7 gram per day) did not change the pH of gall bladder bile in the dog nor did it bring about as great a dissolution of the stones as is noted in the normal and ox-bile fed animal. This dosage of keto bile acids approximated

the human dose. The diluting effect was much less marked than in feeding large doses of ox-bile.

6. The pH of bile is not the sole criterion in the dissolution of gall stones, as is demonstrated by the fact that even though large doses of ox-bile change the pH of dog's acidic gall bladder bile to the alkaline side, they do not significantly influence the degree of dissolution of implanted human cholesterol stones. In our opinion, the dissolution of the stones by the alkaline bile after the feeding of large quantities of ox-bile, is due to its chologogue effect.

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The Effect of Estrogenic Hormone on Gastric Acidity**

By

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and

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THE well known fact that the modal gastric acidity in man is higher than in woman, and conversely the greater frequency of anaecidity in the female (Bloomfield), suggests a possible relationship between sex hormones and gastric secretion. The effect of "Theelin" on gastric acidity has been studied in the dog by Winkelstein, who observed no constant change.

As we were unaware of any similar observations made in man or woman, it was decided to administer Theelin to a group of human subjects. We were particularly interested to see whether or not achlorhydria could be produced.

METHOD USED

A group of twenty individuals was selected, consisting of twelve males and eight females (including six castrates). The ages varied between 23 and 75 years with an average age of 42 years. The patients were ambulatory and reported to the laboratory in a fasting state. They were instructed not to swallow any saliva.

A Rchfuss tube was introduced into the stomach and the fasting contents were withdrawn. One-half mg. of histamine phosphate‡ was given subcutaneously and continuous aspiration carried out in 10 minute periods for a total of one hour. The presence of bile and mucus was recorded.

Prior to the institution of treatment, two or more gastric analyses were done at intervals of 5 to 10 days. During treatment the analyses were continued at intervals of one to two weeks and after treatment at intervals of about two weeks.

The patients were arbitrarily divided into three groups. The first group was composed of nine men who were given relatively large doses of "Theelin" over a short period of time. The group was restricted to men because of their tolerance for larger individual doses of the hormone (Table I). The doses ranged from 4,000 to 20,000 International Units per injection, the usual dose being 10,000 units. The average duration of treatment was 27 days; the average number of injections, 21, and the average duration of study, 9 months (Table 1).

The second group, composed of four women (3 castrates) and three men, received smaller doses of

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TABLE I
Patients receiving relatively large individual doses* of Theelin over relatively short periods

No.	Age	Sex	Diagnosis	Duration of Treatment (Days)	Total Dosage Int. Units	Number of Injections	Number of Gastric Analyses	Duration of Study (Months)	Gastric Acidity Before Treatment	Change in Acidity After Treatment†
1	37	M	Mucous Colitis	32	386,000	31	10	10.5	Normal‡	None
2	51	M	Gastric Neurosis	34	302,000	30	11	8	Normal	None
3	34	M	Duodenal Ulcer	32	264,000	17	19	9	Normal	Increased
4	35	M	Duodenal Ulcer	32	240,000	24	33	12	Increased	None
5	50	M	Hypertrophic Gastritis	26	233,000	18	12	6.5	Normal	None
6	59	M	Gastric Neurosis	31	191,000	18	13	10	Normal	None
7	43	M	Duodenal Ulcer	19	180,000	18	46	13	Normal	Decrease
8	54	M	Atrophic Gastritis	19	145,000	18	15	9.5	Absent	None
9	35	M	Duodenal Ulcer (Gastro-enterostomy)	15	120,000	12	15	4.5	Normal	None
Av.	44.5			27	229,000	21	19	9		

*Average dose per injection: 10,100 Units.

†Free acidity of 60 to 120 cc. of N/10 NaOH is considered normal (following injection of histamine).

‡A change is indicated by an increase or decrease of 20 or more in the average maximum free acidity.

TABLE II
Patients receiving smaller individual doses* of Theelin over relatively longer periods

No.	Age	Sex	Diagnosis	Duration of Treatment (Days)	Total Dosage Int. Units	Number of Injections	Number of Gastric Analyses	Duration of Study (Months)	Gastric Acidity Before Treatment	Change in Acidity After Treatment
†1A	37	M	Mucous Colitis	137	306,000	97	14	10.5	Normal	None
10	33	M	Duodenal Ulcer	142	300,000	100	16	6	Increased	Decrease
11	73	M	"Normal Control"	94	207,000	69	12	5	Decreased	None
12	30	F	Castrate	94	161,000	51	12	3	Increased	Decrease
13	39	F	Hysterectomy	167	118,000	40	6	6	Normal	Decrease
14	25	F	Castrate	61	118,000	40	9	2	Decreased	None
15	29	F	Castrate	64	90,000	30	6	2	Normal	Decrease
Av.	38			105	184,300	61	12	5		

*Average dose per injection: 3,020 Units.

†Previously given larger doses for a total of 356,000 Units (Table I—No. 11).

TABLE III
Patients receiving smaller individual doses* of Theelin over relatively short periods

No.	Age	Sex	Diagnosis	Duration of Treatment (Days)	Total Dosage Int. Units	Number of Injections	Number of Gastric Analyses	Duration of Study (Months)	Gastric Acidity Before Treatment	Change in Acidity After Treatment
16	61	F	Chronic Cholecystitis	30	79,000	27	6	6.5	Normal	None
17	42	F	Castrate	44	65,500	18	13	7.5	Normal	Increase
18	32	F	Castrate	47	66,500	18	16	8	Normal	Increase
19	41	F	Hay Fever	27	59,000	17	12	4.5	Decreased	None
20	40	F	Castrate	25	16,250	18	13	8	Decreased	Decrease
Av.	43			35	57,250	20	12	7		

*Average dose per injection: 2,930 Units.

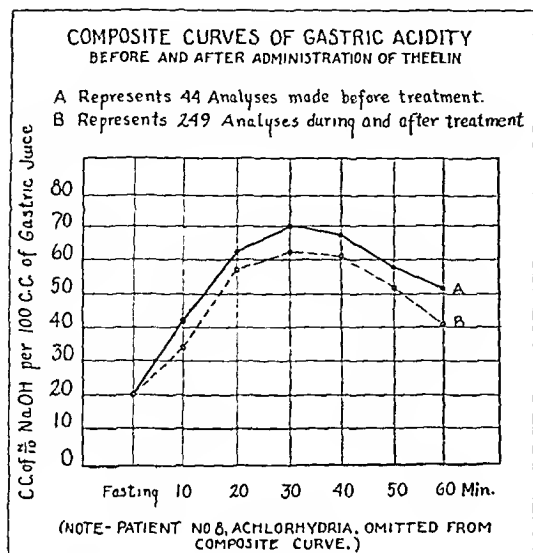


Fig. 1

the hormone over relatively longer periods. The doses ranged from an initial injection of 500 units to one of 4,000 units, with an average of approximately 3,000 units. The average duration of treatment was 108 days; the average number of injections, 61, and the average duration of study, 5 months (Table II).

The last group, composed of five women (3 castrates) received smaller individual doses of "Theelin," but over relatively shorter periods. The doses ranged from 500 to 6,000 units with an average of 2,930 units. The average duration of treatment was 35 days, the average number of injections, 20 and the average duration of study, 7 months (Table III).

A total of 308 gastric analyses was made. The determination of average acidity before and after treatment showed no change in 11 cases, an average increase of 20 or more in maximum acidity in 3, and a decrease of 20 or more in 6 (Table IV). As we have seen even greater changes in acidity following histamine injection occur spontaneously in a trained subject, we are not inclined to attach any significance to such variations. A composite curve made of all the analyses in all the patients (excepting the 15 analyses in the patient with achlorhydria) shows very little variation, although there is a suggestion of a slight decrease in acidity following treatment (Fig. 1).

Of four males with loss of libido prior to treatment, two showed no improvement with reference to this complaint; whereas the other two showed definite improvement during treatment and for some months later. Of two castrates with diminution of potentia

TABLE IV
Effect of Theelin on average maximum free acidity

		No Effect	Rise*	Fall*
Group I	Cases with normal acidity	5	1-(24)	1-(26)
	Cases with increased acidity	1		
	Cases with achlorhydria	1		
Group II	Cases with normal acidity	1		2-(21) 2-(88)
	Cases with increased acidity			2-(55) 2-(25)
	Cases with decreased acidity	2		
Group III	Cases with normal acidity	1	1-(21)	1-(59)
	Cases with decreased acidity	1	1-(21)	

*A rise or fall is indicated by an increase or decrease of 20 or more in the average maximum free acidity, the exact change being included parenthetically.

following recent oophorectomy, one noticed increase of sexual desire whereas the other noticed progressive decrease in spite of treatment. Hot flashes, present in several instances disappeared under treatment.

SUMMARY

The intramuscular administration of Theelin in either relatively large (approximately 10,000 units) or smaller doses (approximately 3,000 units) over periods varying from 15 to 167 days, has no effect on the gastric acidity of man within a total observation period of 2 to 13 months. (Composite curves of acidity suggest a questionable decrease following such treatment).

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Migraine; Epilepsy: Their Association with Hypothyroidism*

By

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THIS report is prompted by the coincident finding of hypothyroidism in a woman and her two daughters. The mother had a history of severe intractable migraine since adolescence, which in early middle life was accompanied by epileptic seizures, and both daughters' early adolescences also were attended by severe and frequent attacks of migraine.

This familial occurrence is not unusual, since hereditary transmission of migraine is unquestioned, and even though Moebius' figure of 90% may be high, certainly Timme's estimate of 50% is conservative, with a far higher maternal than paternal transmission.

The symptom complex of migraine has been the plague of the human race and theory upon theory has been advanced for its causation. We are still confronted by its puzzling etiology—sphinx-like, mute, stubborn and refractory to treatment; often impossible to eradicate. This is not surprising, for migraine, though it may last for many years, has not to date revealed itself in any definite resultant structural change.

The indefinite underlying pathology of this affliction together with its tendency often to disappear spontaneously in later life, allowed a wide theoretical speculative field as to etiology, and can account for the many theories and explanations of the clinical phenomena. Undoubtedly the primary anlage in the hereditary transmission, is an underlying cellular, molecular weakness or an allergy, superimposed on which are the many elements that make for a disturbance in bodily equilibrium.

These elements either singly or in combination, are the exciting causes of the recurrent outbreaks; especially—physical and mental fatigue, disturbance of the special senses, toxic absorption and endocrine dysfunction.

Of all the theories propounded as causative in migraine, in the light of our present day knowledge of functional pathology, the most plausible are allergy and endocrine dysfunction. One is impressed with the striking coincidence of migraine and manifestations of allergy, found, compared with the control group, four times as frequently in the families of patients suffering from migraine. One is also impressed with the basic similarity and behaviorism of migraine to such diseases as asthma, hay fever, urticaria, eczema and serum sensitivity.

The recurrent migrainous explosion, with intervening relatively normal periods, is suggestive of a cumulative effect in its production that could easily fit in with the changing ebb and tide of inter-related function of the secretory glands. The frequency of attacks at the end of menstruation, and the complete disappearance of attacks during pregnancy, are more than coincidentally related to pituitary and ovarian

function. It is also more than coincidence that the migrainous symptoms can be produced by the administration of Follutein; also the frequency of low thyroïdal function present in migraine. Especially noteworthy is the very favorable response of post menstrual and hypothyroid migraine to specific glandular therapy.

In a review of the literature on both migraine and epilepsy, in which basal metabolic rates were estimated, there is preponderance of low readings—both in men and women, especially in the latter.

In the studies reported by Balyeat, Moehlig, Low and Krema, and N. C. Stevens, the preponderance of low basal rates obtained are significant in emphasizing the frequency of hypothyroidism in this disease. Confirmatory also is the increased cholesterol content of the blood, found by Mason and Moehlig. Low and Krema contend that thyroid gland dysfunction or hypofunction may be the basis for the migraine and the prime cause of the allergic manifestations. Also significant, is Stevens' explanation of the production of toxemia in migraine, which likewise places the responsibility on lowered thyroid function. He states—"The hormone of the thyroid gland which regulates metabolism of the body is intimately connected with the nervous, circulatory and digestive systems. If there is an insufficient amount of hormone, the bodily processes are slackened, mentality is sluggish, the pulse is slowed and desire for food diminished. The possibility exists that even the food consumed, is incompletely burned, that the poisonous products of incomplete combustion accumulate in the system, until the limit of tolerance is reached and then an attack precipitated. The toxin then may act anaphylactically or allergically; the thyroid then may undergo a temporary stimulation and for a short time secrete more than its ordinary amount of hormone.

The bodily processes are thus stimulated, with consequent elimination of toxin and with a quick return of the organism to normalcy. This may account for the patient's feeling of well being immediately following the attack, and also for the temporary higher basal metabolic readings. When the thyroid relapses to its former condition of low output, the cycle begins again, to culminate in another periodic explosion."

"A. R.," housewife, age 50, first came under 'my' observation in 1925, with a history of attacks of migraine at 4 to 8 week intervals. These attacks, later increasing in severity and frequency with no apparent relation to menstrual periods which were regular and painless. Past medical history, beyond measles and an occasional head cold, was negative, and the familial background was surprisingly free of migraine and epilepsy. She married at 22—her husband coming from a migrainous family. In the succeeding eleven years, there were born four healthy children; no abortions. There was relative freedom from attacks during pregnancy. At about 38 years of age, the attacks of migraine (previously ushered in by nausea

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and vomiting, vertigo, scintillating scotomata and blurring of vision, followed by severe left temporal and frontal headache) were sometimes replaced by attacks of grand mal with aura of some duration, consisting of nausea and vertigo, and followed by unconsciousness with tonic and clonic spasms.

She had repeatedly, during the preceding 16 years, received the whole gamut of studies, including X-rays of the skull, sinuses, biliary and gastro-intestinal tracts, blood chemistry, cytology, serology, spinal fluid examination and tests for allergy—all with negative results. In addition to symptomatic sedative drugs, many suspicious teeth had been extracted, nasal sinuses intensively treated and eyes frequently re-fracted.

When the patient came under my observation in 1925, examination revealed an intelligent and mentally alert woman of 40. In addition to her persistent attacks of migraine occasionally replaced by epileptic attacks, there were complaints of feeling cold, of abnormal fatigue, of a tendency to moderate constipation, but menstruation was regular and normal. Physical examination, aside from a pair of diseased tonsils and a cardiac rate of 65, B.P. 140/90, was essentially negative.

She submitted to another recheck of all previous studies, also with negative results; and, in addition a basal metabolism reading showed a plus 4% (in retrospect it is noteworthy that this reading was done two days after an attack of epilepsy). A tonsillectomy, elimination diets for minor allergic sensitivity, also colonic irrigations which were popular at the time, were effected—all had but little influence on her attacks. In 1929, on a regular visit to the office, she was in the prodromal state of nausea, and with the mental sluggishness usually preceding an attack. I was struck by an unusual bradycardia—so I ordered a recheck on her basal metabolism, the following morning, which read minus 25%. Thyroid in one grain doses three times a day, retained with difficulty because of nausea, modified and shortened the attack that immediately followed. There was no recurrence of either migraine or epilepsy from 1929 to 1932—during which time her basal metabolic rates were maintained within normal range by from one to one and a half grains of thyroid extract a day.

The patient was not seen during the greater part of 1932. Early in 1933, following an attack of epilepsy, she again came, admitted that over confident, she had not taken thyroid extract for the preceding four months—basal rate then was minus 16%. From that time she has regularly taken one to one and a half grains of thyroid extract a day and her basal rates have varied between minus 8% and plus 5%. Her last basal metabolism reading was minus 1% and her blood cholesterol 184, and she has been well.

Of the four children, the oldest—a girl of 25, and the youngest—a boy of 17, have so far escaped. The second and third children—two girls, both developed migraine.

The older of the two, "J. R." was not suspected of migraine until 1931 because no headache accompanied periodic attacks of nausea, vomiting and epigastric

pain, present since early childhood. One of these episodes in 1928 was followed by dizziness and a mild catarrhal jaundice. All the thorough studies were negative, and no noticeable improvement occurred following removal of tonsils and nasal sinus treatment, together with elimination diets and symptomatic measures. In 1931, at the age of 18, for the first time, severe headaches accompanied these abdominal upsets. Basal metabolism readings at this time were minus 14% and minus 17%, cholesterol 163. Her response to thyroid therapy was as dramatic as her mother's; since then she has been free of both abdominal and cephalic attacks; has completed a college course, is now teaching and entirely well.

In 1932, the younger sister "L." a bright girl of 16, developed typical attacks of migraine similar to her mother's. The outstanding abnormality on complete study was a minus 18% basal metabolism, with a cholesterol of 210. For the past three years, she has been on thyroid therapy, with no return of symptoms, until last September 18th, when mild headache and nausea recurred—persisting for three days before she returned for examination, when her basal metabolic rate was minus 20%. She had not taken thyroid extract all summer because her Camp Doctor volunteered the information that thyroid was injurious to the heart. Upon reassurance, thyroid therapy was resumed, with immediate cessation of the symptoms; her maintenance averages one grain of Armour's Thyroid a day. Her last basal rate was minus 11%.

SUMMARY

1. A woman suffering from migraine and epilepsy had two daughters subject to migraine, one with the abdominal type and the other the cephalic. Hypothyroidism, without the picture of myxedema was found in all three. They promptly responded to thyroid replacement therapy.

2. Of the many theories regarding etiology, the most plausible is, inherited allergic susceptibility with superimposed exciting causes—endocrine imbalance the most prominent. The frequent low metabolic readings are significant of lowered thyroid function. The symptomatic relief produced by Ergotamine Tartrate may be due to its suddenly boosting endocrine function.

3. For the recognition of the hypothyroid state, it is important that basal readings be made as near as possible to an approaching attack and never immediately after.

4. We can only hope for ultimate solution of the migraine problem through coordinated investigations, inclusive of all mechanisms possibly concerned in its production, instead of isolated and fragmentary studies by specialists concerned only with enthusiastic revelations in their respective fields, taking no cognizance of the subtle complexities involved.

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Phenolphthalein

By

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THE toxicity of phenolphthalein has received considerable attention and aroused much discussion. Fantus and Dyniewicz (1) gave one thousand single doses of the drug and collected the urine and conclude that phenolphthalein does not produce albuminuria.

Zoltan von Vamossy (2), who discovered the cathartic action of the drug, insists that it is not harmful in laxative dosage.

Newman (3) collected seventeen types of atypical phenolphthalein skin eruptions as well as other evidences of toxicity such as lipoid nephrosis, toxic nephritis, visceral hemorrhages and ulcerative colitis. He states that "phenolphthalein is contained in more than one hundred and twenty-five proprietary preparations put up in the form of laxative drugs, chewing gums, confections, fruits and biscuits. It is also used for pink icing on cakes, for coloring of candies, and in pink mouth washes and dentifrices. Hence when exudative lesions of obscure origin are present phenolphthalein as the etiologic agent should be considered."

Belote and Whitney (4) list one hundred and three proprietary preparations which contain phenolphthalein. They discuss the pathogenicity of the drug particularly in regard to the skin and mucous membranes.

My experience as a clinician had given me a strong impression that the habitual use of the drug as a laxative is harmful to a large percentage of the patients who employ it. To clarify the matter I examined one thousand consecutive case records of patients who presented themselves to the clinic with symptoms referable to the digestive tract. (Feces analysis is made in each case regardless of the symptomatology). I wished to determine the effects of the continuous daily dose of the drug over a period of two months or more, excluding those cases in which a single dose produced toxic symptoms such as skin eruptions, etc.

The study disclosed that one hundred and seventy-seven patients had taken daily doses of the drug for a period of time varying from two months to two years. One hundred and fifty-two of these patients suffered from catarrhal colitis. Twenty-two of these patients did not present evidence of catarrhal colitis. Three of these patients presented a chronic stomatitis.

Catarrhal colitis is a frequent diagnosis in our clinic. It is characterized by the presence of excess of mucus more or less intimately mixed with the feces, in clumps of which are found, microscopically, pus cells and occasional blood cells. Proctosigmoidoscopy in many of the cases reveals a generally congested mucous

membrane. The patients in whom the feces are not formed and which contain only excess of mucus are not classed as catarrhal colitis. The usual subjective symptoms of catarrhal colitis are fatigue, irregular fecal evacuations, excess of colonic gas, and vague abdominal discomfort: many patients present evidence of malnutrition and weight loss.

Three hundred and seven of the one thousand case reports disclosed catarrhal colitis.

152 cases as stated above were addicted to phenolphthalein.

73 cases of protozoan or flagellate infestation.

9 cases of *Lamblia Giardia* infestation.

10 cases of anacid gastritis.

6 cases of achylia gastrica.

40 cases of addiction to other purgative drugs.

17 cases in which the etiologic factor was not determined.

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Catarrhal colitis produced by purgative drugs is quickly cured by withdrawal of the offending irritant, and proper measures for the restoration of normal colon function.

The cases of stomatitis had been very rebellious to treatment, but responded when the phenolphthalein was discontinued.

CONCLUSIONS

Over fifteen per cent of the patients (177) in the gastro-enterologic clinic employed phenolphthalein as a habitual laxative. In a large percentage (152) a diagnosis of catarrhal colitis was made.

A small percentage (22) had established a tolerance for the drug and exhibited no signs of toxicity. Chronic stomatitis was present in three patients addicted to the drug.

Considering the large number of preparations of phenolphthalein in the market, the physician must be on guard in his selection of laxative drugs. Many of the manufacturers of agar and oil mixtures slip in a dose of phenolphthalein to make the preparation more active, thereby deluding the doctor, who believes that he is prescribing a nonirritant mixture.

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A Study of the Diseases in the Negro with Particular Reference to the Gastro-Intestinal Tract

By

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ALTHOUGH gastro-enterology has made rapid strides in recent years, nevertheless, the exact etiology of most gastro-intestinal diseases still remains obscure. Year by year, fragments of knowledge have been added and various relationships have been shown to exist, but there is not, as yet, sufficient information to definitely point to the causative factors. This study attempts to throw further light upon the predisposing factors of the various functional and organic gastro-intestinal conditions by the method of approach which seeks to evaluate racial and constitutional factors as seen in the Negro. Since chronic peptic ulcer is one of the major concerns of the gastro-enterological internist, particular emphasis will be placed upon it.

A problem of this kind necessarily raises the question whether or not there exists any racial immunity or susceptibility on the part of the Negro to certain diseases. If we believe in the theory of evolution, that all men sprang from common ancestors and that surviving anthropologic forms through natural selection came to possess certain superior attributes, biologically speaking, which allowed them to overcome the stresses and strains of unfavorable environmental influences and to survive at the expense of less adapted environmental types, then it seems that we are justified in comparing the resultant characteristics of the various races with their respective incidence to diseased states, with the hope of finding certain predisposing factors which might affect the susceptibility to these diseased conditions. In other words, autochthony working over thousands of years has evolved groups of people throughout the world who have become distinctive in appearance, in innate characteristics and in their immune reactions to disease-producing agents in their aboriginal environment, and it should be possible to uncover some of these factors. Pearl (1) has presented evidence indicating the great importance of the evolutionary history of the human body in influencing human mortality.

Investigators have been struck with the unusual tendency of the Negro towards certain diseases and with the infrequency with which other diseases manifest themselves in him. A perusal of statistical literature shows a high incidence in the colored of tuberculosis, syphilis, tetanus, keloid formation, uterine fibroids, yaws, sleeping sickness, elephantiasis, etc. On the other hand, there is a noticeable decreased incidence of renal and gall bladder calculi, prostatic hypertrophy, most of the diseases of the alimentary tract, erysipelas, yellow fever, scarlet fever, diphtheria, measles, chorea, toxie goitre, refractive errors, trachoma, ovarian tumor, varicocele, baldness, carcinomata in general, etc. Furthermore, the Negro often reacts differently to his disease. We are all aware of his difference in reaction to tuberculosis, which is apt to be of the rapidly progressing type and in which the evidences of resistance are not marked. Despite the greater incidence of syphilis among the colored, there are relatively few cases of locomotor ataxia among them. Sickle-cell anemia is almost exclusively found in Negroes. Regardless of the cause, there is enough unanimity of opinion among the various writers to dispel any doubt that there exist distinct differences between Whites and Negroes in morbidity and mortality from certain diseases.

Dublin (2) has quoted statistics from the Metropolitan Life Insurance Company showing definite differences in death rate, particularly in certain diseases, between the white and colored races. Pearl (3, 4) has shown from statistics on autopsy material from Johns Hopkins Hospital, that there are distinct differences in the pathology between Whites and Negroes, both in incidence and in organological distribution of pathological lesions. The total mortality in Negroes from diseases of the alimentary tract and its associated glandular organs was proportionately smaller, while that attributable to circulatory and respiratory diseases was higher. Pearl has been impressed with the difference between Whites and Negroes with respect to malignant disease, in incidence and selectivity of organs. He found that malignant tumors and malignant metastases occur relatively more frequently among Whites, and that in Whites the primary growths tend to be more distributed throughout the various organ systems. Although the total number of cancers was relatively smaller in the Negro, the relative incidence in the alimentary and reproductive systems was higher, because cancer in the Negro tends to be concentrated in these two systems. These variations in neoplastic diseases suggest to Pearl that there are biological differences in constitutional pattern between Negroes and Whites.

Love and Davenport (5), army investigators, state that the nervous system of Negroes shows fewer cases of instability than that of the Whites, and that the incidence of functional disturbances in the Negro is comparatively low. Rosser (6) has emphasized the racial predisposition of the Negro to develop adult connective tissue, and he has called this the "fibro-plastic diathesis." He notes that in protologic cases this tendency is manifest as external fibrous growths and internal fibrous strictures, so commonly seen in Negroes. Rosser also points out the infrequency of hemorrhoids in Negroes. Miller (7) and Alsbrook (8) have noted gynecologic differences between Whites and Negroes. Paskind (9) concludes from a comparative study of the action of atropine in the white and colored races, that the Negro is less susceptible to the central action of atropine, as evidenced by a slower response in the change of the heart rate.

This qualitative and quantitative variation of the Negro in reaction to various diseases entails for its proper elucidation a careful analysis of all possible differences that may exist between the Negro and the Caucasian—anthropological, anatomical, psychological, pathological, environmental, social, economic, etc.

ANTHROPOLOGY OF THE NEGRO

The Negro race, as we know it, is one of the three outstanding divisions of the Negroid stock (10). The other two divisions are the Oceanic Melanesians and the Dwarf Black or Negritos. Certain skeletal remains of the so-called Grimaldi race, which flourished during the Aurignacian period of the Old Stone Age are probably evidences of a Negroid stock. Neither the ancestors nor the descendants of these early peoples have been traced, but the discovery of the remains indicates a differentiation of the type at a period antedating the birth of Christ by some

TABLE I

	Case	Sex	Age	Primary Diagnosis	Secondary Diagnosis	BP	Acid	Lues	Remarks
1	114430	F	33	Duodenal Ulcer	Chr. gastro-duodenitis. Gastrectasia	140 90	6 7	Pos.	Several admissions. Gastro-enterotomy
2	103809	M	38	Duodenal Ulcer	Pyloric obstruction	120 80	100 145	0	Improved
3	116580	M	40	Duodenal Ulcer	C.N.S. Lues (?)	150 95	65 88	Pos.	Gastritic evidence on G.A. & X-ray. Improved
4	114538	F	30	Duodenal Ulcer	Chronic gastritis Duodenal ileus	120 85	37 57	N.R.	Gastritic evidence on G.A. & X-ray. Improved.
5	108476	M	50	Duodenal Ulcer	Chronic gastritis Diabetes mellitus Coronary sclerosis	140 90	10 60	0	Improved
6	107150	M	54	Duodenal Ulcer	Chronic gastritis Pos., Ca. of stomach	120 70	65 85	0	Obstr. signs. Unimproved. Refused surgery
7	112970	M	41	Duodenal Ulcer	Chronic gastritis	N.R.	55 89	0	Improved
8	69490	F	39	Duodenal Ulcer		120 78	55 80	0	5 prior adm., 3 c hematemesis. Gastro-enterotomy. Refused further surgery
9	114428	M	38	Duodenal Ulcer	Chronic gastro-duodenitis. Dis. tonsils	102 70	88 112	0	Operated for perforated duodenal ulcer several yrs. before
10	97024	M	15	Duodenal Ulcer (?)		98 70	30 35	N.R.	Deformity of duodenal cap, but diag. not absolute. Improved
11	121833	F	63	Duodenal Ulcer	Chronic gastritis	N.R.	89 106	N.R.	Evidence of gastritis on G.A., X-ray and gastroscopy
12	118007	F	26	Duodenal Ulcer	Chr. gastro-duodenitis. Chr. P.I.D.	126 88	85 95	N.R.	Many admissions. Obstructive symptoms
13	72814	M	36	Duodenal Ulcer	Chronic gastritis Duodenal stasis	120 90	96 138	Pos.	Many admissions. Gastroscopy done
14	119795	M	28	Duodenal Ulcer	Intercostal neuralg. scoliosis. Lues	115 65	83 100	Pos.	Improved
15	126204	M	58	Duodenal Ulcer	Chronic gastritis	168 100	84 92	0	2 adm. c hematem. Obstr. symp. Refused surgery
16	124333	M	37	Duodenal Ulcer	Chronic gastritis Lues	124 74	12 58	Pos.	Improved
17	112654	M	48	Duodenal & Gastric Ulcer	Chr. gastro-duodenitis. Lues. Pyloric	170 112	93 104	Pos.	Gast. ulcer near pylorus. Pt. sclerotic. Refused operation
18	80957	M	30	Duodenal & Gastric Ulcer	Lues	N.R.	100 120	Pos.	Oper. for peptic gast. ulcer few years before
19	121844	M	30	Duodenal & Gastric Ulcer	Chronic gastro-duodenitis. Lues	130 105	42 54	Pos.	Obstr. symp. Gastrectomy after several adm.
20	112613	F	53	Gastric Ulcer	Hypertensive and Arterioscler. Ht. Dis.	204 125	N.R.	0	Very arteriosclerotic. Improved
21	112619	F	31	Gastric Ulcer	Healed pulmonary tuberculosis	150 140	N.R.	0	Adm. c hematemesis. Improved
22	117066	M	40	Gastric Ulcer	Peritonitis	N.R.	N.R.	N.R.	Adm. c perforation. Died following oper. Cancerous nests in ulcer tissue
23	121825	M	51	Gastric Ulcer	Lues	95 70	N.R.	Pos.	2 adm. Course of disease very suggestive of gastric lues

twenty to twenty-five thousand years. The relationship of this primitive group to the other races has not been made out.

According to the Spanish historian, Las Casas, quoted by Matas (12), the first Negro slaves who were introduced from Africa to the New World were landed in Santo Domingo in 1505. With the exception of some tribes of Caribs that still inhabit the Gulf coast of Central America and some islands of the Caribbean Archipelago, all the Negroes on the American Continent are directly descended from the black slaves imported from Africa during the slave trade (12). The history of the Negro in the United States dates back to August, 1619. A great many Negro sub-groups were introduced into the American Colonies—the Senegalese, Yolloff, Bambara, Mandinga, Congo or Guinea, Arada, Caffre, etc.—and these types differed slightly in their physical and mental characteristics. The four classes of Negroes today are principally the Guinea Negro, the Yolloff, the Caffre and the mulatto. The relatively pure African types are, however, extremely rare because there has been such a great intermixing of these types, both amongst themselves and between the white race. It has been estimated that out of the twelve million or more Negroes in the United States, ten million are mulattoes (13).

Most anthropologists deny that there is such a thing as a pure race. Boas (14), who is one of the principal proponents of this contention, points out, that from a purely biological point of view, there is no such a true concept as race unity. He goes on to say: "The multitude of genealogical lines, the diversity of individual and family types contained in each race is so great that no race can be considered as a unit. Furthermore, similarities between neighboring races and, in regard to function, even between distant races, are so great that individuals cannot be assigned with certainty to one group or another." Taking this factor into account plus the tremendous miscegenation which has occurred in the past two hundred years, one is obliged to use the term "race" in only its broadest sense when referring to the Negroes as a distinct group. We regard and classify a person as a Negro when he has the slightest trace of negroid characteristics, which are dominant according to Mendelian inheritance, even though he possesses seven-eighths of white blood and reacts to all intents and purposes as a Caucasian. Whenever, therefore, the term "Negroes" or "Negro race" is used in this discussion, it is to be understood that what is meant is a group, highly mixed in racial stock and ancestry, who possesses the so-called negroid characteristics.

ANATOMICAL PECULIARITIES

Most of the anatomical peculiarities of the Negro are readily recognizable and constitute the chief elements for what we know as negroid characteristics. The Negro is usually tall in stature, and has a narrow head and prognathous jaw. The skin is dark brown, the hair is woolly and makes a close curl, the sclerae are muddy, the lips are thick and fleshy and the nose is broad and flat. The auditory canal is usually very straight. The sweat glands and sebaceous glands are highly active. The excessive activity of the sebaceous glands gives a peculiar oily lustre to the skin, and this oily exudation has a very strong odor, which is strongest in the most robust. The subcutaneous layer is thick, and the submucous connective tissue is more developed (12).

In addition to the more or less obvious anatomical differences between Negroes and Whites, statistical data reveal that in the Negro the chest circumference is somewhat less (owing to a reduction in anterior-posterior diameter), the nipples are slightly higher, the pelvis is narrower, the iliac crests are lower, the suprasternal notch is slightly higher, the extremities are relatively longer, the hair line is lower on the forehead, and the interocular breadth and interpupillary distance are greater (15). Todd (15) has shown that certain physical features of the Negro, mostly

in the face, are relatively little altered by interbreeding with other human stocks. He calls these "entrenched Negro features" and cites, as examples, the nasal breadth, the thickness of the lips, the mouth width, the interpupillary distance and the ear height. On the other hand, pigmentation, head breadth, total facial height and nasal height are readily modified by hybridization. Herskovits (16) has also pointed out from physical measurements on large numbers of Negroes that there is a large degree of homogeneity in spite of the great intermixing which has occurred.

Bean and Baker (17) have reported that the spleen is smaller in Negroes. This has been confirmed by Pearl and Bacon (18) and later by Moon (19). Bean and Baker (20) have also reported that the liver is smaller in Negroes than in Whites. Bean (21), in a comparative study of White and Negro brains, found certain racial differences, but these differences could not be verified by Mall (22).

The deep pigmentation of the skin, which is so striking in the Negro, is not fully understood. It consists of pigment granules distributed throughout the lowermost layers of the epidermis. There is estimated to be about one gram of this pigment, melanin, in the whole skin of a Negro (23). Melanin is an amorphous, organic, colloidal dyestuff which contains the indole ring. It is insoluble in water and in organic solvents. It is capable of reducing certain metallic salts, particularly silver nitrate. The melanin-producing cells, melanoblasts, contain a ferment, an oxidase, which is the sine qua non in melanin formation (24, 25, 26, 27). According to Bloch (25), this ferment converts the colorless substance, 3, 4—dihydroxyphenylalanine, which he has called "dopa," to melanin, which colors the cell black (dopa reaction). This particular ferment, dopa-oxidase, is specific for dopa only, and is present exclusively in cells of melanin-producing tissue (25, 27). Whenever dopa-positive cells are increased in number, we have an increased activity of pigment formation, and vice versa (27). The darker the skin, the more abundant are the dopa-positive cells. Thus in the Negro the dopa-positive cells are very numerous, while in the albino, they are absent. The ultimate source of melanin, directly or indirectly, is probably tyrosine (24). A relation between melanin formation and the endocrine glands is suggested by the increase in skin pigmentation which so frequently occurs during pregnancy. There appears to be a very close resemblance, perhaps an identity, between the raw material for the manufacture of melanin and that which forms adrenaline (23, 26). Melanin is highly dependent upon the suprarenal glands, and it is probable that when adrenaline is not formed, pigment appears in its place, as for example, in tuberculosis of the suprarenals.

PSYCHOLOGICAL TENDENCIES

Many writings have appeared in the literature recently stressing the relation of psychogenic and neurogenic factors to various diseases, and it becomes necessary to consider the psychological reactions of the Negro, in order to see what effect they might have upon influencing his autonomic and cerebro-spinal nervous mechanism.

Odum (28) concluded from his study that the Negro easily responded to pleasurable stimuli in an impulsive way, but that he lacked perseverance and self direction and was more or less indifferent to anything bordering on the profound.

Matas (12), in a very extensive paper on surgical peculiarities of the Negro, was impressed with the unique reaction of the Negro to operations. He believed that there is a lessened sensibility of the nervous system on the part of the Negro to pain and shock, but that the emotional side is well developed, and that there is in him a certain tendency to fatalism which leads him to accept accidents and illness with all their consequences as parts of the inevitable. Furthermore, he believed that there is a native

TABLE II

	Case	Sex	Age	Primary Diagnosis	Secondary Diagnosis	BP	Acid	Lues	Remarks
24	89912	F	37	Chronic Gastritis Hemorrhagic	Duodenal ulcer? Gastric ulcer? Lues	120 80	17 38	Pos.	Sev. adn. c. hematem. Pyloric ulcer suggested, not proven. Luetic factor may play important role
25	100231	M	40	Chronic Gastritis	Achlorhydria Lues	200 135	0 15	Pos.	Possible luetic factor. Improved
26	101613	F	35	Chronic Gastritis	Gastro-intestinal allergy	150 100	N.R.	0	Gastroscopic confirmation. Improved
27	124334	F	70	Chronic Gastritis	Irrit. colon c. colon stasis	110 76	29 38	0	Improved
28	113601	F	44	Chronic Gastritis	Marked oral sepsis	118 70	39 60	0	Hist. suspicious of ulcer. X-ray showed marked hypertr. rugae
29	91069	M	26	Chronic Gastro- duodenitis	Lues	135 85	25 50	Pos.	Improved. Signed release after several days
30	99636	F	55	Chronic Gastro- duodenitis	Gastric lues?	N.R.	0 20	Pos.	X-ray showed pyloric defect, regressed after anti-luetic therapy
31	99942	M	25	Chronic Gastro- duodenitis	Lues	128 80	N.R.	Pos.	Improved
32	118690	M	48	Chronic Gastro- duodenitis	Pyelonephritis, kinked appendix, poss. early term. fistula	140 100	N.R.	Pos.	X-ray suggests mucosal changes at terminal ileum
33	121817	M	35	Chronic Gastro- duodenitis	Lues, acute hallucinosis (Schizophrenia?)	138 70	0 24	Pos.	Not completely studied. Signed release
34	117549	M	41	Gastritis, probably luetic	C.N.S. lues?	128 76	5 10	Pos.	X-ray defect regressed aft. anti-luetic ther.
35	121810	F	35	Pep. ulcer syn. Etiol. undeter.	Poss. gall bladder path., diabetes mcl.	160 125	N.R.	0	Not completely studied. Signed release
36	96362	F	32	Acute Gastritis		110 75	N.R.	0	Cause undetermined. Rapid improvement
37	107286	F	22	Acute Gastritis	Lues	110 80	15 35	Pos.	Cause undetermined. Rapid improvement
38	81093	F	40	Acute Gastro- enteritis		115 80	N.R.	0	Food poisoning
39	100974	M	20	Acute Gastro- enteritis	Lues	100 70	N.R.	Pos.	Dietary indiscretion
40	111985	M	20	Acute Enterocolitis	Possible bacillary dysentery	N.R.	N.R.	0	Etiology uncertain. Pt's brother was said to have dysentery
41	101452	F	22	Acute Enterocolitis	Polyposis of colon	55 70	N.R.	0	Etiology uncertain
42	94318	F	28	Gastric Stasis	Pylorospasm. Chronic P.I.D.	110 80	30 55	0	Pyloric spasm may be reflexly caused by chronic P.I.D.
43	118891	F	43	Gastric crisis of tabes dorsalis	Chronic gastro- duodenitis	152 110	29 35	Pos.	X-ray showed marked distortion of gastric rugae. Alcoholic hist.
44	106399	F	40	Pyloric Stenosis, cause undeter.	Peritonitis	114 80	20 50	0	Gastric obstr. Resembling malign. Dev. peritonitis and died
45	108491	F	32	Vomiting, etiology undetermined		N.R.	N.R.	N.R.	Not completely studied; signed release
46	106121	F	24	Duodenal Stasis	Poss. Gastric ulcer	109 70	0 35	0	X-ray suggested poss. gastric ulcer

and characteristic indifference, which more certainly relieves the Negro from worry as to the future than is likely to be the case with the white man.

Beckham (29), of Howard University, mentions what he calls the "Negro complex." "This complex is not necessarily identical with inferiority complex," he says: "It is an emotional sublimation that enables the Negro to escape dire reality. In this state he is able to simulate happiness."

Many psychological tests have been employed to obtain scientific confirmation of psychological racial differences, but there is no unanimity of opinion among authorities either as to the value of these tests or as to their interpretation. Klineberg (30) calls attention to many factors, independent of race, which may account for some differences in the results of various investigators—familiarity with the English language, culture, social and economic status, rapport between subject and the one administering the test, motivation (is the subject doing his best?), factor of sampling, etc. Darrow and Heath (31) could find no relation between temperamental type, as defined by questions used in psychological tests, and physiological responses to various stimuli, as measured by galvanic skin reflex, blood pressure, respirations, etc.

Patrick and Sims (32), after administering psychological tests to Negro and White college students in four universities, including two Negro universities, conclude that there are statistically reliable race differences between the Negroes and the white group in introversion. They find that there is a tendency for Negroes to be less introverted and more dominant than the white group. Hurlock (33), in testing White and Negro boys of the seventh and eighth grades, using a modification of the Downey Will-Temperament Test, finds that White boys are speedier in decision and movement and possess greater volitional perseverance than Negro boys, but that Negro boys, on the other hand, possess greater self confidence, finality of judgment, motor inhibition and power of coordination of impulses. She concludes, on the basis of her findings, that differences in temperamental traits do exist between Negro and White children. The results of McFadden and Dashiell (34) are very similar, but the differences are not as marked.

Davenport (35) concludes from his studies of fairly large samples of Whites and Negroes, living under similar social and economic conditions and having about the same amount of scholastic training, that there are distinct differences in mental output between these two races. He believes that these differences are racially innate, and are probably dependent upon differences in the structure of the sense organs and nervous system, which do not reveal themselves as readily as the physical differences.

Although psychological racial differences are not marked and clear-cut, yet there is sufficient data to indicate that there is a tendency toward unique psychological responses in the Negro race.

ENVIRONMENTAL AND RELATED EFFECTS

The Negro seems evolutionally attuned to torrid geographical regions and can work in many places where the White cannot, for he is relatively immune to heat stroke and sun stroke. Taylor (36), who has written many articles on the Negro in relation to his health, has stressed that the Negro is unfit to live in cold climates and doesn't flourish well above the Mason and Dixon Line.

Huntington (37) has shown that there is a distinct relationship between human activity and climate—where the weather and temperature is more variable (stimulating), there tends to be greater human activity, energy and achievement. He points out that the native races within the tropics are dull in thought and slow in action, and that a change, an overstimulation, has occurred in those Negroes who have gotten away from their indigenous environment. He believes that just as the White men do not react well to the tropics, so is there an unfavorable re-

sponse of the Negroes to more stimulating climates. Dowd (38) has noted a relationship between psychological reactions of the African Negro and the climatic zone in which he lives. It has been succinctly said that climate calls the tune to which living creatures dance.

Mills (39) has stressed the importance of climatic factors in various diseases. He is of the opinion that individuals have optimum climates to which they are best suited, and that a stimulating climate, where there is a great variability of the weather and temperature, causes, in those unacclimated or unfitted, an excessive environmental excitation of bodily function. This, he believes, eventually produces general physiological exhaustion which becomes manifest in various diseased conditions, such as exophthalmic goitre, pernicious anemia and diabetes. Mills also points out variations in the female sex function with variations in climate. Englemann (40) has shown a trend toward earlier puberty for Negroes as one passes from the tropics up through the southern and central states to New England, with its greater temperature and weather variability. It indeed appears likely that too violent a climate can produce functional hyperactivity, especially of the nervous and endocrine system.

Wood, Jones and Kimbrough (41) have found geographical variations in the incidence of heart disease. They report that rheumatic heart disease is almost twice as common in Massachusetts as in Virginia, but that hypertension as an etiologic factor is somewhat more prevalent in the latter state. These authors also report that organic heart disease is almost twice as common in the Negro as in the White, but that the reverse is true in angina pectoris, despite the fact that syphilis and arteriosclerosis are such important etiologic factors in cardiac disease in the Negro. It is interesting in this connection to note that Johnson (42) found slightly more than one-third as many cases of marked coronary sclerosis, in autopsy records of patients above the age of 39, in Negroes as compared to Whites.

Diet certainly plays a tremendous role in influencing the state of health of an individual, but just how great a factor it is in inducing certain clinical entities, particularly diseases of the digestive tract, is very difficult to evaluate. McCarrison (43) has advanced the hypothesis that many of our present-day gastro-intestinal disorders are due to faulty food, which has come about by our highly civilized methods of living. It is interesting that in the nine years that he spent in the midst of several isolated races in a remote part of the Himalayas, far removed from the refinements of civilization, he never saw among them a case of asthenic dyspepsia, peptic ulcer, appendicitis, mucous colitis or cancer, although he performed on the average of 400 major operations yearly. He noted that these natives used no alcohol and very little sugar, and that they subsisted mostly on milk, eggs, grains, fruit and vegetables. Because of economic reasons, one of these groups moved to another geographical section where simple fresh foods were not as easily obtainable, and McCarrison was surprised to observe that they soon developed disorders which were previously unknown to them. McCarrison is of the opinion that a faulty diet is not the basis of such disturbances as diarrhea, dysentery, gastric and duodenal ulcer, intussusception, gastric dilatation, colitis and failure of colonic function. He has performed animal experiments which give further evidence in this regard. Boland (44), who has reviewed a large series of white and colored patients in the South, reports that in Whites the incidence of appendicitis is six times that of the Negro, while the incidence of peptic ulcer is twice as great and that of biliary tract disease is ten times as great. He agrees with McCarrison, and attributes these differences to a more wholesome diet of the southern Negroes—a diet which he says is similar to that of McCarrison's East Indians.

While it cannot be denied that diet plays an important

TABLE III

	Case	Sex	Age	Primary Diagnosis	Secondary Diagnosis	BP	Acid	Lues	Remarks
47	117347	F	55	Duodenal Diverticulum	Cholelithiasis	140 70	N.R.	0	Symptoms suggested pep. ulcer. Signed release, studies not complete
48	93610	F	43	Duodenal adhesions cause undetermined		120 56	20 40	0	Not completely studied. Signed release
49	115749	M	61	Carcinoma of stomach		110 50	0 21	0	Cach. death. Pyloric involvement with liver metastasis
50	94851	F	54	Carcinoma of stomach		122 74	0 60	0	Laparotomy confirmed pyloric involvement
51	94852	M	47	Carcinoma of stomach		112 98	0 25	0	Inoperable CA of fundus and pars media. Gastro-tomy done
52	100139	F	50	Carcinoma of stomach		N.R.	0 27	0	Refused operation
53	102763	M	65	Carcinoma of stomach		110 85	0 10	0	Inoperable lesion with liver metastasis
54	99863	M	36	Carcinoma of stomach	Poss. gastric lues	N.R.	0 15	Pos.	Refused operation
55	100735	M	51	Carcinoma of stomach	Poss. traction diverticulum of jejunum	80 60	0 7	0	Subtotal gastrectomy
56	100610	M	55	Carcinoma of stomach		150 90	0 15	0	Cach. death, with widespread metastasis
57	100327	M	40	Carcinoma of stomach		N.R.	15 50	Pos.	Subtotal gastrectomy
58	123830	M	42	Carcinoma of stomach	Chronic gastritis, Coronary disease	110 60	0 20	N.R.	Cach. death with aortic involvement and pulmonary metastasis
59	105942	M	54	Carcinoma of esophagus		140 110	N.R.	0	Lesion at level of supra-sternal notch. Gastro-tomy done
60	125793	M	50	Carcinoma of esophagus	Lues, Megacolon	110 70	26 41	Pos.	At junction of middle and lower third
61	125738	M	49	Diaphragmatic eventration?	Chronic gastritis, Art. scl. heart disease	190 90	12 24	0	Dysphagic symptoms slightly improved
62	100278	M	31	Catarrhal jaundice	Quest. duodenal ulcer second portion	130 75	N.R.	0	Improved
63	109324	F	33	Catarrhal jaundice		105 60	N.R.	0	Died 2 weeks. Autopsy. Liver necrosis on autopsy. Etiology obscure
64	109312	F	42	Catarrhal jaundice	Possible gall bladder pathology	145	N.R.	0?	Hist. of iustic ther. Wess. & Kahn are negative
65	116576	M	37	Catarrhal jaundice	Lues, Poss. hepatic lues	N.R.	41 59	Pos.	Alcoholic history. Improved rapidly
66	116577	M	30	Catarrhal jaundice		N.R.	60 76	0	Rapid improvement
67	94549	M	27	Catarrhal jaundice	Primary lues	125 85	N.R.	Pos.	Penile chancre on adm. Jaundice cleared rapidly
68	95182	F	22	Catarrhal jaundice	Lues, Poss. iustic hepatitis	N.R.	N.R.	Pos.	Galactose test positive. Improved rapidly
69	112557	F	33	Catarrhal jaundice	Lues	116 50	40 60	Pos.	Rapid improvement

part in producing gastro-intestinal derangements, yet the differences in the incidence of diseases between Negroes and Whites are so great and so consistent, even in large urban communities where the Negro of necessity eats the food of modern civilization with his white neighbors, that it is extremely unlikely that dietary factors can account for the statistical variations. Rivers (45), in studying a group of Negroes in central Texas, was impressed with the rarity of peptic ulcer syndrome among them, yet he found that their diet was unbalanced, they ate whenever they could and whatever they could get, they lived under pathetic hygienic conditions, they dissipated recklessly, their habits invariably included the abuse of tobacco and alcohol and their hours of sleep were very irregular.

Although social and economic factors do not concern us much in a study of this kind, nevertheless, they do exert considerable weight indirectly. Many of the factors previously mentioned are obviously greatly influenced by social and economic conditions. Herskovits (46), who has probably made the most comprehensive study of the physical anthropology of the American Negro, points out that there is even a social factor in the formation of the type of the Negro. He finds that for the most part dark Negroes marry light-colored women, and he believes that this is due to the conscious or unconscious desire for light skin, which becomes synonymous with social elevation, lack of prejudice and greater opportunity.

It appears from statistical and other evidence that a change has been gradually occurring in the incidence of various diseases in the colored race. The general morbidity and mortality were less than that of Whites in the South during the whole period of slavery, up to the time of emancipation, but there has been a great increase since 1864, and now the rates for the Negroes are generally higher than those of the Whites (2, 12).

Miscegenation with the White race no doubt plays a large role in these variations. The opinion has been expressed by many writers that hybridism greatly increases the general susceptibility to diseases. Matas (12) has found that dental caries and alveolar abscesses are relatively rare in the dark Negro but common in the light mulatto, and he also expressed his belief that syphilis is less virulent and less fatal in relatively pure Negroes. Hoffman (47), discussing race amalgamation, said: "Whatever the race may have gained in an intellectual way, which is a matter of speculation, it has been losing its greatest resources in the struggle for life, a sound physical organism and power of rapid reproduction."

Hoffman (48) has very comprehensively reviewed the racial factors in cancer, and points out, that although malignant tumors were very infrequent in the slave population and are rare in practically all parts of present-day Africa, the present cancer mortality in the Negro is rapidly rising and is approaching that of the Whites. Tuberculosis was said to be unknown among the savage tribes of black men that inhabit the meagerly-explored regions of equatorial Africa, and among those who lived on the coast of Guinea in the early days of the slave trade before colonization by white men (12). Although recent figures show a decline in morbidity and mortality rates from tuberculosis in Negroes, there is still more than two and a half times the incidence in Negroes as compared to the White race. Similar changes are apparent in hypertension. Donnison (49) rarely saw hypertension in an African native, but reports now indicate the great incidence of this condition in American Negroes (41, 50, 51, 52). Pollock (53) has indicated the relative and absolute increase of mental diseases in the Negro in the United States from 1910 to 1923, especially in the North. Although diabetes mellitus was formerly a rather uncommon condition in Negroes, the mortality rate is now almost that of the Whites (2). Leopold (54) shows evidence that in the female sex diabetes is even slightly more common in the colored race. Similarly cases of hemophilia (55) and

pernicious anemia (56) in the Negro have recently been reported in the literature, but there is some doubt whether these conditions have ever been seen in a relatively pure-blooded Negro, although the case of hemophilia reported by Crandall (55) may be one of these extremely rare cases. Cases of Addison's disease in the Negro have also recently appeared in the literature (57), bringing the total number of reported cases to fourteen. It arouses speculative interest that, although tuberculosis is the etiologic factor in the vast majority of cases of Addison's disease and in spite of the great incidence of tuberculosis among the colored population, Addison's disease in the Negro is extremely uncommon.

The Negro is becoming more and more a part of the hustle and bustle of modern civilization, with its increasing responsibilities, greater psychic and mental stimulations and faster methods of living, and it is very likely that this is an important factor in the increasing incidence of certain diseases among Negroes. The opinion expressed by Moschowitz (58), that such diseases as essential hypertension, Graves syndrome, gastric and duodenal ulcer, cardiospasm and irritable colon are of psychogenic origin, is very persuasive and is corroborated to a certain degree in the Negro, in that these diseases have steadily shown an increase in the colored race since the abolition of slavery when the Negro has had to compete with the Whites in the economic struggle for existence.

STUDY OF CASES

The records of all Negro patients admitted to the gastro-intestinal service of the Graduate Hospital of the University of Pennsylvania during a five year period were completely surveyed. During this period the total number of admissions to the Graduate Hospital on all services was 37,324. Of this number 7,480 (20%) were colored patients, of which 4,529 (12%) were females and 2,951 (8%) were males. The total number of admissions to the gastro-intestinal service during this time is, unfortunately, not easily available. The total number of colored gastro-intestinal patients who were studied during this period was 115 (Tables I-V incl.), and this represents many and multiple readmissions, many of these patients, especially those with peptic ulcer, having been admitted more than three times during the five years. These patients have been divided into groups, showing the sex ratio, average age, and percentage of each group (Table VI). Although these patients constitute the vast majority of colored patients admitted to the hospital with gastro-intestinal symptoms, yet it should be pointed out that some patients with digestive disorders may have been on other services (medical, surgical, etc.), either because the digestive complaints were minor to some other complaint or else because of a mistaken diagnosis at time of admission. Nevertheless, it is felt that this data represents a cross section of the gastro-intestinal diseases in the colored race in Philadelphia. It is unfortunate that the material from which this data is drawn does not allow a differentiation between relatively full-blooded Negroes and mixed bloods, and it is hoped that in the future this discrimination will be made.

Considering the number of patients studied, regardless of the number of admissions, the Negroes constituted 27% of carcinomata of the stomach (Whites 27, Negroes 10), 13.5% of duodenal ulcers (Whites 121, Negroes 19), 16.6% of gastric ulcers (Whites 37, Negroes 7), 7.3% of cholelithiasis (Whites 101, Negroes 8) and 11.1% of idiopathic ulcerative colitis (Whites 32, Negroes 4). Taking into account that the

TABLE IV

	Case	Sex	Age	Primary Diagnosis	Secondary Diagnosis	BP	Acid	Lues	Remarks
70	110687	F	25	Catarrhal jaundice	Lues	100 72	28 39	Pos.	Rapid improvement
71	121822	M	43	Catarrhal jaundice	Lues, Rheumatic heart disease	152 90	39 56	Pos.	Rapid improvement
72	125658	F	17	Catarrhal jaundice		130 48	17 40	N.R.	Rapid improvement
73	109234	F	29	Hepato-cellular jaundice, arsenical		120 80	N.R.	Pos. ?	Jaun. dev'd after intensive anti-luetic ther. Wmss. & Kahn neg.
74	115819	F	22	Acute cholecystitis	Cholelithiasis Lues	115 90	N.R.	Pos.	Cholecystectomy after anti-luetic therapy
75	109279	F	27	Cholelithiasis	Chr. Cholecystitis	120 70	N.R.	0	Cholecystectomy
76	108124	M	53	Cholelithiasis, common duct	Aortic sclerosis	135 75	N.R.	0	Improved. Refused surgery
77	109265	F	39	Cholelithiasis	Chr. Cholecystitis	130 85	N.R.	0	Cholecystectomy
78	98231	F	31	Cholelithiasis	Chr. Cholecystitis	118 75	N.R.	0	Cholecystectomy. (Reoperated 2 years later, adhesions)
79	122723	F	46	Cholelithiasis	Chr. Cholecystitis Lues, achylia gast. (histamine)	N.R.	0 11	Pos.	Refused surgery
80	121803	F	33	Cholelithiasis	Chr. Cholecystitis Lues	140 100	13 32	Pos.	Refused surgery
81	125566	F	50	Cholelithiasis & cystic duct block	Chr. Cholecystitis	N.R.	N.R.	0	Cholecystectomy
82	96437	F	55	Chr. cholecystitis	Pericholecystic adhesions. C. V. renal D.	170 110	30 60	0	Cholecystectomy, no stones found
83	123878	F	48	Carcinoma-head of pancreas	Diabetes Mel. Cardio Vasc. Renal Disease	170 104	32 48	0	Cholecysto-gastrotomy
84	125700	M	54	Carcinoma of pancreas, met. to stomach & liver	Perforation of CA of stomach, tabes, optic atrophy	180 80	36 56	Pos.	Wide-spread meta. Gastric malign. ruptured. Died after laparotomy
85	125608	M	54	Carcinoma of head of pancreas with meta. to liver		132 78	N.R.	Pos.	Cholecysto-duodenostomy
86	101925	F	45	Portal cirrhosis with ascites	Lues, Colonic Diverticulosis, Umbilical hernia	112 85	35 65	Pos.	Little improvement. Signed release after one month
87	116683	M	45	Toxic cirrhosis	Primary CA of liver. Lues Hypoproteinaemia	100 70	37 53	Pos.	Persistent ascites. Died after rev. adm. Autopsy showed beginning CA of liver
88	100577	F	33	Colon Stasis	Lues	110 85	N.R.	Pos.	Pain right side and headache. Slight improvement
89	92904	M	20	Colon Stasis	Poss. duodenal ulcer, Lues	126 80	20 35	Pos.	Improved
90	125762	F	73	Irritable Colon	Hyperten. and Art. Scl. heart disease. Tertiary lues. Cataract, O.D.	200 104	N.R.	Pos.	Studies failed to show suspected malignancy. Improved
91	100907	M	48	Colonic diverticulosis	Lues Luetic heart dis.	200 125	N.R.	Pos.	X-ray also shows colonic irritability and spasm
92	115970	M	64	Diverticulitis & diverticulosis	Art. Scl. heart dis. Lues	180 110	62 75	Pos.	Improved

TABLE V

	Case	Sex	Age	Primary Diagnosis	Secondary Diagnosis	BP	Acid	Lues	Remarks
93	113605	F	60	Colonic Diverticulosis	Art. Scl. Heart Dis. Esophagitis	170 108	42 62	0	Improved
94	103580	F	57	Polyposis of colon c malig. degen.	Metastasis to liver and other viscera	124 76	0 15	0	Died following operation
95	108127	F	60	Intes. Obstr. c Perf. Jejun. Ulcer	Colonic Diverticu- losis. Jejunal Diverticulum	135 85	N.R.	N.R.	Died soon after adm. Autop. showed 3 jejunal ulcers, one perf.
96	108908	M	37	Intes. Obstr. Small bowel p. op.		130 80	N.R.	0	Adhesions from previous opera- tion
97	110276	M	35	Intermit. small bowel obstr. p. op.	Incisional hernia	125 85	24 29	Pos.	Adhesions from previous opera- tion
98	105799	F	32	Idiopathic ulcer. Colitis, chronic	Nutritional Edema	100 74	20 45	0	Died after several months. Autop. conf'd diagnosis
99	108130	F	32	Idiopathic ulcer. Colitis, chronic		116 70	35 60	0	Improved
100	93589	M	57	Idiopathic ulcer. Colitis, acute		164 98	N.R.	0	Somewhat atypical course. Improved
101	109326	F	16	Idiopathic ulcer. Colitis, chronic	Chr. Nastroitis	N.R.	N.R.	0	Died following mastoidectomy
102	97507	F	32	Amoebic Dysentery	Lues	118 68	23 30	Pos.	Amoeba recovered in stools
103	98501	M	42	Tabes Mesenterica		148 100	15 40	N.R.	Huge retroperiton. Mass on oper. (Tbc.) X-ray therapy
104	117550	M	46	Tbc. of intes. lymph nodes, liver and sem. vesicles	Lues, Peritonitis Mucoid Adeno- carcinoma of stomach	140 75	0 16	Pos.	Died several weeks after exploratory. Autop. conf'd diagnosis
105	108501	M	26	Tuberculous peri- tonitis		110 65	15 30	0	Liver tests nega- tive. Exploratory revealed true diag. Improved
106	108509	M	27	Chronic peritonitis, probably tubercu- lous	Ascites Lues	140 88	0 45	Pos.	Liver tests nega- tive. Refused exploratory laparotomy
107	108505	F	25	Generalized miliary tuberculosis	Toxic cirrhosis, Tbc. hepatitis, Pleurisy	95 65	N.R.	0	Autop. showed ex- tensive miliary Tbc.
108	126125	M	41	Acute Appendicitis	Lues Trau. Cataract, O.S.	120 75	N.R.	0?	Treated conserva- tively. Improved
109	112959	F	36	Lymphopathia Ven- with rectal stric- ture	Partial intes. obst. Recto-vag. fistula Ventral hernia	114 78	N.R.	0	Frei test positive
110	109381	F	27	Lues	Colonic Diverticu- losis. Poss. Hep. lues	120 90	8 24	Pos.	Prim. Diagn. of lues due to mult. of symp.
111	109283	M	60	Lues	Portal cirrhosis? Hepatitis-luetic? Pulmonary Tbc.	148 100	25 45	Pos.	Prim. Diagn. of loes due to mult. of symp. Died later of cereb. thromb.
112	108480	M	49	Hyperten. and Card. Vasc. Renal Dis.	Tertiary lues	195 155	37 53	Pos.	Adm. c. vomiting and weakness. Improved
113	112644	M	50	Ruptured Aortic Aneurysm	Lues Pulmonary Tbc.	96 60	N.R.	Pos.	Admitted with dys- phasic symptoms. Autop. done
114	109399	M	40	Pellectra	Alcoholic Gastritis. Food Deficiency	135 110	0 31	0	Admitted with vomiting. Died shortly thereafter. Autopsy
115	112625	F	28	Hypothyroidism	Gastric atony and Stasis. Lues	104 70	N.R.	Pos.	Adm. with hist. suggesting G.B. pathology

Negroes constituted 20% of the total number of admissions, these figures tend to show a greater incidence of gastric carcinoma and a lower incidence of peptic ulcer and ulcerative colitis in the colored race, while there is a marked decreased incidence of cholelithiasis in the Negro. There was only one Negro patient out of the 115, in whom a primary diagnosis was made of a functional disturbance. The rarity of mucus and spastic colitis and of the various gastro-intestinal neuroses in Negroes seen at the Graduate Hospital in previous years has been mentioned before (59).

Many writers, particularly in the South, have noted the infrequency of peptic ulcer in the Negro (44, 45, 51, 60, 61, 62, 63, 64). However, Steigmann (65), in a recent study at Cook County Hospital, found no appreciable racial difference in the incidence of peptic ulcer, and he believes that the Negro is just as susceptible as the white person when he is subjected to the same environmental, psychogenic strains, such as are present in industrial centers. Jaffe (66), working in the same hospital, found on autopsy material that, although peptic ulcer was a more frequent cause of death among white people, there was about the same incidence on routine autopsies. The probable reasons for this variation in statistics will be alluded to later.

Many theories have been advanced to explain the genesis of peptic ulcer, and these have been briefly summarized by Stix (67), as follows: (1) Gastritis theory, first advanced by Cruveilhier in 1829 (Proponents: Konjetzny, Faber, Korbsch, Puhl, Kalina, etc.). (2) Neurogenic theory, first advanced by Rokitsansky about 1845 (Proponents: V. Bergman, Cushing, Westphal, Robinson, Levison, etc.). (3) Circulatory theory,

first advanced by Virchow in 1853. (4) Mechanical theory (Aschoff, Bauer). (5) Infectious theory (Roscnow, Billings, Passler). (6) Peptic theory (Buchner, Sippy). (7) A combination of two or more theories (Rivers, Westphal, V. Bergman, Krehl, etc.).

In all probability peptic ulcer is a constitutional and systemic derangement, in which gastric manifestations are predominant. Rivers and Vanzant (68) have pointed out that many patients who first present themselves with symptoms of peptic ulcer do not have peptic ulcer, but are of the same type in which peptic ulcer is found. These patients often turn up later on with demonstrable peptic ulcer. The relation of body type and constitutional build to various diseases, which was first brought to attention by Stiller (69), has been stressed by Draper (70, 71) and others with regard to peptic ulcer. However, Feigenbaum and Howat (72), after evaluating their anthropometric studies, do not believe that there are distinctive, anatomic characteristics of patients with either peptic ulcer, cholecystitis or diabetes mellitus. Nevertheless, regardless of body type, it is well-recognized that peptic ulcer is generally associated with an unstable vegetative nervous mechanism, in which the parasympathetic division is usually predominant.

The familial tendency to develop peptic ulcer is well known and suggests a genetic factor. Dickinson (73) has cited five children in the same family with peptic ulcer, all of them being of the asthenic habitus. Meyer, Maskin and Necheles (74) found in testing the gastric acidity of 82 healthy relatives of ulcer patients that most of them exhibited either too little free acid or too much free acid.

Rivers (45) has thoroughly discussed the factors in

TABLE VI

Disease	No. of Cases	% of Group	Sex		Average Age
			M	F	
Duodenal Ulcer	15	13.8	11	5	39.1
Gastric Ulcer	4	3.5	2	2	43.7
Duodenal and Gastric Ulcers combined	3	2.6	3	0	36.0
Chronic Gastritis	11	9.6	6	5	41.5
Malignancy	16	13.8	12	4	51.1
Acute Digestive Upset	6	5.2	2	4	25.0
Gastric, Duodenal, or Colon Stasis	4	3.5	1	3	25.0
So-called Catarrhal Jaundice	11	9.5	5	6	30.9
Primary Liver Disease	3	2.6	1	2	39.7
Gall Bladder Disease	9	7.8	1	8	39.5
Tuberculous Involvement	5	4.4	4	1	33.2
Ulcerative Colitis	4	3.5	1	3	34.3
Intestinal Obstruction	3	2.6	2	1	44.0
Colonic Diverticuli	3	2.6	2	1	57.3
Duodenal Diverticulum	1	0.8	—	1	55
Amoebic Dysentery	1	0.8	—	1	32
Gastric Crisis of Tabes	1	0.8	—	1	43
Irritable Colon	1	0.8	—	1	73
Acute Appendicitis	1	0.8	1	—	41
Miscellaneous	12	—	5	7	—
Total	115	—	59	55	—

the genesis of peptic ulcer, and emphasizes the ambitious, intensive, and high-strung characteristics of peptic ulcer patients. The Negroes, as a general rule, as has been previously brought out, are not of this type, but it is certainly conceivable that under increased environmental stimulations, they may react inwardly and outwardly as violently as anyone else, and thus predispose themselves to various psychogenic disorders. Differences in reactivity, in emotional responsiveness and in temperament are only differences in threshold or degree and an emotionally sluggish person will respond as intensely as the most extreme individual of the opposite end of the distribution

curve, provided the stimulus is sufficiently raised (13).

Psychogenic factors in the production of peptic ulcer have been stressed in many recent writings (45, 58, 63, 64, 65, 75, 76, 77). In fact, Robinson (78), giving an etiological classification of gastro-duodenal ulcerations, even suggests substituting the term "psychogenic ulcer" for common chronic peptic ulcer. That emotional disturbances have a profound effect on the various functions of the body has been emphasized by Cannon (79), Alvarez (80, 81) and others. Pavlov (82) demonstrated psychic effects on the physiology of digestion in animals long ago. It is doubtful, however, whether animals ever develop chronic peptic ulcer

TABLE VII
Peptic ulcers in previous five year period not recorded before

	Case	Sex	Age	Primary Diagnosis	Secondary Diagnosis	BP	Acid	Lues	Remarks
1	80063	M	48	Duodenal Ulcer	Spontaneous Pneumothorax	$\frac{130}{70}$	$\frac{80}{95}$	0	Disch. as imp. after 1 month. Spont. pneumothorax, prob. Tbc.
2	85942	M	58	Duodenal Ulcer		N.R.	$\frac{100}{120}$	N.R.	Pt. very art. scl. Looks older than stated age. Obstructive symptoms
3	85468	M	40	Duodenal Ulcer		$\frac{140}{84}$	$\frac{35}{60}$	0	Discharged as imp. after two weeks
4	91937	M	38	Duodenal Ulcer	Pyloric Obstruct.	N.R.	$\frac{45}{65}$	Pos.	Hist. of recurrent attacks. Operated in another hosp. for excision of ulcer
5	88512	F	21	Duodenal Ulcer	Chronic P.L.D. Lues	$\frac{125}{80}$	$\frac{120}{185}$	Pos.	Discharged as imp. after one month
6	89949	F	24	Duodenal Ulcer		N.R.	N.R.	0	Adm. c. hematem. Pt. signed release after 1½ weeks. Not comp. studied
7	71603	M	41	Duodenal Ulcer		$\frac{110}{72}$	$\frac{65}{95}$	0	Pt. later dev. a perforation. Died following op. Autopsy done
8	76474	M	56	Duodenal Ulcer	Hypertensive Heart Disease	$\frac{204}{120}$	$\frac{60}{80}$	0	Discharged as imp. after two weeks
9	60746	F	19	Duodenal Ulcer	Chronic Tonsillitis	N.R.	$\frac{65}{100}$	0	Discharged as imp. after 2½ weeks
10	58584	M	32	Duodenal Ulcer	Chronic Tonsillitis	N.R.	$\frac{75}{95}$	Pos.	Discharged as imp. after one week
11	75088	F	38	Poss. Duodenal Ulcer		N.R.	$\frac{40}{65}$	0	Hist. suggestive of duod. ulcer. Pt. signed release
12	58794	M	45	Duodenal and Gastric Ulcer		N.R.	$\frac{20}{45}$	0	Adm. several times. Finally had gastro-enterostomy
13	67223	M	29	Mesenteric Tbc.	Duodenal Ulcer. Pyloric Obstr. Lues	N.R.	$\frac{45}{75}$	Pos.	Autopsy confirmed diagnosis
14	79461	F	29	Gastric Ulcer		$\frac{120}{80}$	$\frac{30}{40}$	Pos.	Had a gastro-enterostomy 10 years before
15	90637	M	38	Gastric Ulcer	Pyloric Stenosis	N.R.	$\frac{45}{60}$	0	Discharged as imp. after three weeks
16	74046	F	50	Gastric Ulcer	Colon Stasis. Aortic Sclerosis. Lues	$\frac{118}{84}$	$\frac{50}{75}$	Pos.	Discharged as imp. after three weeks
17	58327	M	32	Gastric Ulcer	Lues	N.R.	$\frac{60}{80}$	Pos.	X-ray somewhat sugg. of gastric ulcer. Pt. signed rel. Was not re-rayed

as we know it in man, although Fox (83) has described ulcers in captive wild mammals, particularly in Primates and Carnivora, which resemble human peptic ulcer. There seems little doubt that psychogenic factors are definitely related to peptic ulcer, and if we are to believe that the Negro is innately less responsive to psychogenic influences, then we would expect to find a decreased incidence of peptic ulcer in the colored

39 years of age showed evidences of arteriosclerosis, and only three of these were luetic. In three out of the four patients who had both gastric and duodenal ulcers there was a positive Wasserman.

Bockus (59) has pointed out that peptic ulcer symptoms in the Negro are usually less classical, and that the amount of pathology found at operation and autopsy is often greater than what one might expect.

TABLE VIII
40 patients with peptic ulcer

	No. of Cases	Sex		Aver. Age	No. with Gastritis	No. c Lues	Obstr. Symptoms	Perforation	Hemorrhage	Operation
		M	F							
Duodenal Ulcer	28	19	9	40.0	15	8	8	2	3	5
Gastric Ulcer	8	4	4	40.5	4	4	1	2	1	3
Duodenal and Gastric Ulcer Combined	4	4	0	38.3	3	3	3	1 (gastric)	0	3
Total	40	27	13		22	15	12	5	4	11

race. In order to get a more accurate estimate of peptic ulcer in the Negro, additional cases were taken from the previous five year period, which had not been recorded in the later years (Table VII). The total number of ulcer patients during the ten years, regardless of the number of admissions, was forty (Table VIII). There were 28 cases of duodenal ulcer (19 males, 9 females), 8 cases of gastric ulcer (4 males, 4 females) and 4 patients in whom both gastric and duodenal ulcers were at some time found (all males). The ages ranged from 15 to 63 and were quite dispersed throughout all the age groups. There was a slight tendency for an increased incidence in the older ages, eleven (27.5%) being 48 or over. The average age for the duodenal ulcer group was 40.0, that for the gastric ulcer group was 40.5, while in the patients having both gastric and duodenal ulcers, the average age was 38.3. The majority of these ulcer patients, especially those in the later years of this study, when we have become more "gastritis conscious," showed evidences of chronic gastritic changes, as evidenced by a dirty gastric residuum containing many epithelial and pus cells, by fuzziness and irregularity on roentgenographic examination, and in many cases by gastroscopic appearance. Five of the patients (12.5%), all males, had at some time an acute perforation of their ulcer (3 gastric, 2 duodenal). Four patients (10%), 1 male and 3 females, were admitted with gross bleeding (3 duodenal, 1 gastric). Twelve patients (30%) had evidences of pyloric obstruction (8 duodenal, 1 gastric, and 3 with combined ulcers). Eleven of the patients (27.5%) at some time underwent an operation for their ulcer. There was nothing characteristic or remarkable about the blood pressures. On gastric analysis most cases showed varying degrees of hyperchlorhydria, while the remaining ones exhibited generally a high normal free acid. There were no cases of achlorhydria, and in only one case was there less than a normal acidity. Sixteen of the patients had a positive Wasserman reaction, eighteen showed no evidences of lues, and there was no record of the remaining six. The ulcer patients with lues occurred mostly in the younger age group. Most of the patients passed

He has also been impressed with the greater frequency with which syphilis and tuberculosis act as causative factors in producing pathology in the upper gastrointestinal tract in Negroes, even though these lesions are rare. Bockus doubts if he has ever seen peptic ulcer in a pure-blooded Negro, who did not have in association either advanced gastritis, syphilis, marked arteriosclerosis or tuberculosis (94).

Although syphilitic lesions are rare in the gastrointestinal tract, one often wonders what part syphilis may play as a predisposing factor to other conditions or in influencing certain diseases, such as peptic ulcer, with which it may be coincidentally associated. It is interesting that visceral syphilis, except cardiovascular involvement, practically never occurs concomitantly with para-luetic manifestations (tabes or paresis) (95). In the present series of 115 cases, 50 cases showed definite evidence of syphilis, 3 cases were questionably luetic. 52 cases showed no evidence of involvement and 10 cases were not recorded. In nine cases in which syphilis was associated it was felt that the luetic factor played some part in the symptomatology. (Cases 23, 24, 25, 30, 34, 65, 68, 110 and 111). Bockus and Bank (96) have reported cases of upper gastro-intestinal diseases associated with syphilis which did not respond well until after anti-luetic treatment was instituted. They have emphasized the multiplicity of X-ray findings and the presence of retention or stasis in the terminal esophagus or terminal duodenum in those cases in which the lues is playing an active part.

There were ten cases, in this colored series, of carcinoma of the stomach, 8 males and 2 females. The ages ranged from 36 to 61, most of them being around the fifth decade. The average age was 49.1. Nine of these patients showed an achlorhydria, while in the remaining one there was a hypochlorhydria. In most of the cases the lesion was in the antral part of the stomach. All cases showed rather advanced lesions. Fitts (97) has also pointed out the infrequency of finding early gastric carcinomata in the colored race, and, in his

comparative series of White and Negro cases, the Negroes showed more frequently an absence of free hydrochloric acid.

The low incidence of cholelithiasis in Negroes, found in this study, has been often noticed (12, 42, 98, 99, 100). Jaffe (99) has reviewed the literature from various countries, and finds statistics which show that the Negroes and lesser pigmented races all have a lowered incidence of cholelithiasis. He also shows, as do most writers, that cholelithiasis is very infrequent among colored males. In the present series seven cases out of eight were in females.

Eleven cases of so-called catarrhal jaundice were seen during the five year period (5 males, 6 females). Of this number, six showed evidence of lues, while in one the luetic factor was questionable. The ages ranged from 17 to 43, most cases falling between 25 and 35. The average age was 30.9.

SUMMARY AND CONCLUSIONS

Evolution has gradually evolved races of men who are distinctive in appearance and state of reactivity to external influences. Each race has therefore acquired certain tendencies, whereby it is not only able to function best in its indigenous environment, but by means of which it is either able to withstand unfavorable environmental influences or else by which it is made more susceptible to them. These innate biological possessions are present in all men, they differ in all persons only in degree and they tend to be more alike in a given race. In other words, just as races have certain physical peculiarities which distinguish them, so do they also have unique methods of reacting to all of their surroundings.

The Negro, over hundreds of generations in his aboriginal environment, has acquired particular characteristics in appearance and response. He shows anthropological, anatomical, psychological and pathological differences from the white man.

A study of 115 cases of Negroes on the gastro-intestinal service has revealed the following observations:

1. Compared to the white group during the same period there is a slightly lower incidence of duodenal ulcer, a considerable decrease in incidence of idiopathic ulcerative colitis, and a marked decreased incidence of functional disturbances and cholelithiasis. On the other hand, there is a higher incidence of gastric carcinomata in the colored group.

2. In peptic ulcer there was a tendency for more frequent occurrence in the later ages, most cases showed a hyperchlorhydria, and there were evidences, in the majority of cases, of chronic gastritic changes in association. Lues was more frequently associated with gastric ulcer. Acute perforations occurred only in males.

3. In almost all of the cases of gastric malignancy far advanced lesions and achlorhydria were found.

4. Nearly half of the patients showed definite evidence of lues, and in a certain number of cases it was felt that the lues played some part in the symptomatology.

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A Practical Method for Determining the Concentration of Buffer Salts in the Body Fluids

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It has long been known that an animal maintained on a full diet from which, however, the buffer salts have been removed will die more quickly than a control animal which receives no food at all. The reason why these buffer salts are so important is because all of the physiologic processes depend upon definite and constant conditions of pH. Trypsin, for example, finds its optimal action at pH 6 to 8, while pepsin cannot function except in the presence of hydrochloric acid at about pH 1.5 to 2. Clinicians have long known that many of the functional disturbances, the pathologic physiologies such as allergy, were secondary to disturbances in the relative concentration of the serum buffer salts. There is urgent need for a practical test for determining the buffering ability of the body fluids.

The concentration of the buffer salts in the blood is always constant and can be determined by chemical methods; however this necessitates 13 different, complicated determinations which makes routine practice clinically impractical. Because the cells of the salivary glands, the stomach, the pancreas, and the kidneys are selective, the normal buffering mechanism of the blood cannot be studied by an analysis of their respective secretions and excretions. The only organ

NOTHING in the animal economy is more constant than the H ion concentration of the blood and fluids which bathe the tissues. When different amounts of acid or alkali are added to water the range of H ion concentration is very extensive, whereas the blood and body fluids remain constant, notwithstanding the continual addition of acids and alkalies from food, and acids which form as a result of metabolism.

The mechanism by which this constancy of pH of the blood and body fluids is maintained is the buffering action of the salts normally contained in these fluids, viz., an acid group, chlorine, iodine, phosphorus, silicon and sulphur, and an alkaline group, aluminum, calcium, copper, iron, magnesium, manganese, potassium and sodium. All of these buffer salts are always present in a definite and constant concentration. When the H ion concentration of the body fluids changes, dissociation of these buffer salts maintains a constant pH of 7.2. The range of the normal buffers is approximately from pH 7 to pH 7.6. As long as the change in H ion concentration remains within this physiological range, it is "compensated" by the normal buffers; when the range is greater than can be corrected by the normal buffers it is "uncompensated."

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in which the secretions and excretions are constantly buffered at pH 7.2, as in blood, is the colon.

EXPERIMENTAL

Instill into the colon, through a urethral catheter, 4 ounces of water at pH 7.2 (neutral). Permit the water to remain in the colon for 20 minutes, then remove and determine (electrometrically) the pH. Normally, it will always be found at pH 7.2.

If 4 ounces of water at pH 10 (alkaline) is instilled and removed in 20 minutes, the pH again will be found at pH 7.2.

If now 4 ounces of water at pH 3 (acid) is instilled and removed in 20 minutes, the pH likewise will be found at pH 7.2.

In short, the mucosa of the normal colon, in the presence of a normal concentration of buffer salts in the serum, maintains the secretions of the colon and the feces constantly at pH 7.2. This experiment can be shortened by simply instilling water at pH 7.2. If upon removal it is found to have remained at pH 7.2, the normal buffering mechanism of the colon is functioning. On the other hand, if the pH of the returned fluid has changed either to the acid or alkaline side, a failure of the buffering mechanism is indicated.

The same experiment can be conducted by instilling a solution of *any known pH* between pH 3 and 10. Normally, in 20 minutes, the pH will be buffered at pH 7.2.

UNCOMPENSATED ALKALOSIS

(Mr. B. N.) Chronic Diarrhea.

Instillation of solution pH 7.2; twenty minutes later, pH 7.6. Instillation of solution pH 10; twenty minutes later, pH 8. Instillation of solution pH 3; twenty minutes later, pH 7.6.

In this case it will be noted that pH is always overcorrected on the alkaline side, indicating a preponderance of alkaline salts which are uncompensated by acid buffer salts. This is a case of uncompensated alkalosis.

UNCOMPENSATED ACIDOSIS

Instillation of solution at pH 7.2; out in 20 minutes—pH 3.2. Instillation of solution at pH 10.5; out in 20 minutes—pH 7.2. Instillation of solution at pH 3; out in 20 minutes—pH 3.2.

In this case there is a failure of the alkaline salts, indicating uncompensated acidosis.

In summary, if a solution at any pH between pH 2 and 10 is instilled into the colon, the normal buffering mechanism of the colonic mucosa will correct it to pH 7.2 if it can; if the serum buffer salts are available in normal concentration. Failure of the buffering mechanism indicates an imbalance in the relative concentrations of the normal serum buffer salts. It should be noted that failure of the buffering mechanism does not necessarily indicate a *reduced* concentration of the acid or alkaline buffer salts, but more often an imbalance in the relative concentrations between the acid and alkaline groups.

However, the above tests are inconvenient and too

time-consuming for routine practice. An easier way to determine the buffering mechanism of the colon is to determine the pH of *fresh feces*. The reaction must be taken immediately after passage of the feces; if feces is permitted to stand an hour, acids and alkalies which no longer come under the buffering action of the colonic mucosa are rapidly formed, making such determination entirely incorrect. Fresh feces can be obtained in the office by injecting an ampule of pitressin.

Because it is thin and therefore easily and quickly affected by a minimum of moisture, litmus paper is the quickest way in which to determine the pH of the feces. If the litmus paper is made up at pH 7.2 (neutral) it is extremely sensitive. It is not necessary to insert the litmus paper *into* the feces, thereby obscuring the color changes; simply to bring one side of the paper into contact with the feces is sufficient. The reaction is easily read on the opposite side of the paper. If the reaction to litmus is amphoteric, the normal buffering mechanism is functioning and nothing more need be done. If the reaction is acid or alkaline (blue to red or red to blue) the buffering mechanism is unbalanced and the exhibition of the normal buffer salts is indicated.

If an exact (quantitative) determination is desired, or if fresh feces cannot be conveniently obtained, the instillation of solution of known pH as described above, must be done. However, for practical purposes it is only necessary to determine the reaction of fresh feces to litmus paper, as the treatment is the same whether the imbalance is on the acid or alkaline side. It has been shown that an uncompensated imbalance of the buffer salts can only be corrected by the exhibition of *all* of the serum salts. The absorption of these salts is regulated by a mechanism which is chemically mutually interrelated, so that the administration of one of them (only) often results in the further elimination of other salts of the group (Macleod). Likewise, pediatricians have long known that the absorption of iron is facilitated by the presence of calcium. If all of the normal buffer salts are exhibited in their relative concentrations as in blood, the normal physiologic relationships are reestablished.

The author has found, however, that if these salts are given by mouth in too great concentration, even though the relative concentrations are quantitatively correct, adverse osmotic pressures are set up in the colon which interfere with absorption. Studies are now under way to determine the proper concentration in which these salts must be administered to be absorbed. This test likewise offers a convenient means for studying the relationship between the serum buffer salts and acid achylia and hyperacidity of the stomach. If this test, which requires but one minute is routinely done, many obscure cases will be found to be secondary to uncompensated acidosis or alkalosis. Further studies along this line will be reported in a later paper.

CONCLUSION

A practical method is described for recognizing uncompensated acidosis and alkalosis.

Terminal Ileitis: Conservative Surgical Treatment

By

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IN any disease in which we are ignorant of the etiologic factors, the method of treatment must of necessity be empiric. In the past few years since the appearance of a paper by Crohn and his collaborators, the medical profession has come to recognize as a clinical entity the disease which is now commonly known as regional or terminal ileitis. The etiology of this disease is still unknown, although Felsen (2) considers it part of the group of intestinal inflammatory lesions caused by the atypical dysentery bacillus of Sonné Duval. Because of our lack of definite knowledge of the causative factors, we must fall back upon our clinical experience in formulating the proper therapeutic procedures. Fortunately our knowledge of the pathology of this disease is much more comprehensive.

In the advanced chronic cases we have a clear cut picture in which the following changes predominate. The bowel segment proper has become reduced in caliber. Its soft, supple, consistence has become converted into a rigid induration as a result of the development of a considerable amount of fibrous tissue. As a result of this cicatrization, the lumen of the bowel is markedly diminished and it is this change that produces the characteristic X-ray picture described by Kantor (1). Sinus tracts, having their origin in the ulcerated and necrotic mucosa, penetrate the wall of the bowel and enter (1) into the mesentery producing mesenteric abscesses, (2) into adjacent loops of bowel which have become adherent to one another, (3) into the peritoneal cavity itself where small intra-abdominal abscesses are found, or (4) into the abdominal wall proper, producing abdominal wall abscesses, which generally rupture externally and form the outlet for the original intestinal sinus. The pathologic changes develop slowly thus allowing for the formation of adhesions prior to the development of the necrotizing intestinal sinus formation with its resultant intra-abdominal abscesses and intestinal fistulae.

When the surgeon is confronted with such a picture, there is practically unanimous agreement regarding the method of treatment to be pursued. The changes produced are such that a restitution of the diseased tissue to normal is out of the question. There remains nothing but the excision of the diseased area. Whether this is performed in one or more stages depends upon the general condition of the patient and the character and extent of the lesion. The treatment, however, calls for radical surgery.

The picture in the early or acute case is an entirely different one. Here we have a diffuse oedema of all the layers of the intestinal wall producing a bowel segment one and a half times the size of the normal bowel. The normal color is markedly changed to that of a dull, lusterless, reddish gray. The consistency is that of a

rigid garden hose. The mucous membrane proper shows irregular areas of ulceration and necrosis. The corresponding portion of mesentery is markedly thickened and oedematous and contains large, soft, hyperplastic lymph nodes. In these early cases there may be a considerable amount of clear, straw colored fluid free in the peritoneal cavity. Here the surgeon is confronted by a problem very much different from that which obtains in the chronic advanced case.

There are two schools of thought regarding the proper method of handling the situation. One group maintains that these early acute cases will invariably continue in their inflammatory and necrotic changes and that therefore the proper method of treatment consists in the radical removal of the diseased segment. The other school holds the opinion that many of these early cases can and do undergo spontaneous resolution and that a restitution to normal does occur. For that reason, this group maintains that it is not only worth while but even more advisable to employ conservative surgical measures such as enterostomy or ilio colostomy. This is done with the idea of putting the diseased inflamed bowel at physiological rest, thus giving the natural reparative agencies of the body an opportunity of performing their function. If the disease process can be arrested and cured by this means, this procedure would be ideal. If it does not produce this desired result, and resection is necessary, this can always be done more safely and at more propitious time at a second stage. How frequently and in what type of case, conservative surgery will produce a cure, we will learn only from clinical experience and especially from a meticulous follow-up over a long period of time.

It is for this reason that the report of the following cases should prove of interest and of some value.

The first case to be reported occurred in 1931 before the clinical entity of regional ileitis was described. The patient was a child, twelve years old, who was under the care of his family physician for a period of four weeks for what was diagnosed as intestinal influenza. The chief complaint during this period was indefinite diffuse abdominal pain and general malaise. This was accompanied by nausea and by a low grade fever rising to 101 in the afternoon. About twenty-four hours before his admission to the hospital (Patient: T. R., No. 340971, Mount Sinai Hospital, July 12, 1932) he was seized with a very severe attack of lower abdominal pain that settled in the right lower quadrant of the abdomen. This pain persisted up to time of operation. Physical examination revealed the following: markedly pale, sallow child, who appears washed out. Localized tenderness over McBurney's point, definite spasm over the lower half of the right rectus muscle and rebound tenderness. No mass could be felt.

At operation, July 12, 1932, the appendix was found considerably elongated and oedematous. The distal eight inches of ileum was markedly thickened and rigid throughout, grayish red in color and lusterless in appearance. The appendix was removed and since the bowel proximal to

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the inflamed terminal ileum showed no distension, nothing further was done. The post operative course was uneventful and the patient was discharged on the sixteenth day post operative. He has been kept under observation up to the present and there has never been any sign of a recurrence or of a recrudescence of the ileitis.

The second case also occurred in the pre "regional ileitis" period. The patient was 61 years old and for several years had been subject to irregular attacks of pain in the right lower quadrant of the abdomen. He was under the care of Dr. A. A. Epstein who treated him on the basis of mild attacks of appendicitis. His last attack occurred on August 29, 1931. This attack was more severe than usual and he was admitted to the Mount Sinai Hospital September 3, 1931 Patient: J. G., No. 329771) with diagnosis of acute appendicitis. Physical examination yielded spasm of the lower half of the right rectus muscle. There was definite tenderness over McBurney's point. Rebound tenderness was present, especially marked in the right lower quadrant of the abdomen. On rectal examination, a boggy induration could be felt in the right fornix. At operation September 3, 1931, a pseudo myxomatous peritonitis with a ruptured mucocele of the appendix was found. In addition to this, "examination of the intestine showed a loop of small gut about two feet from the ileo-caecal junction which had been in contact with the appendix to be thickened about one-quarter to one-half inch over a distance of about six inches. This thickening spread over the free part of the gut in an irregular fashion so that in places it entirely surrounded the gut and in others was just about three quarters of an inch wide. There was complete lack of elasticity of this portion of the bowel, color was markedly red, no glistening appearance could be seen anywhere and it was covered with a moderate amount of fibrinous exudate. In order to forestall what looked like an inevitable intestinal obstruction as a result of this indurated and apparently parietic gut, an enterostomy was performed about one and a half feet above this area in perfectly normal intestine." This patient has also shown no recrudescence or recurrence of the intestinal lesion up to the present time.

The third case was that of a 48 year old man who was admitted to the Beth Israel Hospital on November 12, 1935 (Patient: M. H., No. 78269). For about eleven months prior to his admission to the hospital he suffered from indefinite attacks of pain in the epigastrium and right lower quadrant of the abdomen. These attacks came on at irregular intervals and had no relation to meals or physical exertion. There was no associated disturbance in the genito-urinal tract. Soon after the onset of these attacks of pain, he noticed a "lump" in the right lower quadrant of his abdomen. This lump was not tender and grew larger very slowly. With the onset of the pain, he noticed a gradual and progressive loss of strength, accompanied by a loss of about forty pounds in weight. At the time of admission to the hospital he presented as the outstanding features on physical examination, a marked asthenia, moderate cachexia, definite signs of loss of weight and a fixed painless mass about the size of a fist in the right lower quadrant of the abdomen. A preoperative diagnosis of carcinoma of the caecum was made and the patient was prepared for operation. This was performed on November 12, 1935. When the peritoneal cavity was opened a free, straw colored fluid was found filling the depth of the

pelvis. Caecum and ascending colon normal in every respect. Appendix small and atrophic, without signs of infiltration. Distal two inches of ileum was soft and normal in appearance. From this point on for a distance of fourteen inches the ileum was doubled upon itself and was about two times the caliber of the rest of the ileum—so much thickened that its lumen could not be felt and the peritoneal coat was dull, dark reddish gray with extremely marked injection of the vessels. The corresponding mesentery was thick, friable and markedly oedematous. Proximal to this portion was a stretch of ileum about eight inches long which was perfectly normal in every respect. Proximal to this normal portion, was a stretch of ileum exactly similar to the inflamed part described above—this was about ten inches long. From there on the rest of the bowel was perfectly normal in appearance and on palpation. Owing to the poor general condition of the patient and to the intensely acute nature of the disease process, it was decided to perform a side tracking operation and to delay for a second stage, the resection of the inflamed bowel if this should prove necessary. The ileum was cut completely across about eight inches proximal to the inflamed tissue to assure a healthy area for the line of incision. The distal end of the bowel was now closed with three layers of inverting sutures and the proximal end was anastomosed to the hepatic extremity of the transverse colon by an end to side anastomoses. The first three post operative days were rather stormy and presented the characteristic picture of a paralytic ileus. With this period over, the rest of the convalescence was uneventful. On the tenth post operative day the abdominal mass could scarcely be felt and on discharge from the hospital on the fourteenth day, all that could be made out in the right lower quadrant was a feeling of increased resistance. This patient has been followed up to date for a period of sixteen months and when last seen was free from all pain, had regained his lost forty pounds and was pursuing his usual rather arduous occupation. No mass could be felt in his abdomen.

SUMMARY

Three cases of terminal ileitis are reported. In one of these the appendix was removed but the diseased bowel was left undisturbed. In a second, the treatment consisted of an enterostomy and in the third the treatment instituted was a side tracking ileo colostomy. These cases have been followed up for periods of five and a half, four and three-quarters and one and a quarter years respectively and in none of these has there been either a recurrence or a recrudescence of the inflammation. While it is true that three cases do not constitute enough from which to draw any general conclusions, I feel that many others must have had similar experiences and that only by an accumulation of the experiences of many surgeons, will the profession acquire the mass of clinical knowledge and experience upon which to formulate proper methods of treatment for this disease.

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Karaya Gum as a Mechanical Laxative

An Experimental Study on Animals and Man

By

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and

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OVER a period of years many different substances have been offered for the management of chronic constipation. Physiologic knowledge and clinical experience have caused a reduction in the use of mineral and vegetable substances which produce their effect by increasing the force and rapidity of peristaltic movements. Instead, there has been an increase in the use of bland, indigestible substances which increase the bulk and moisture of the feces, or which serve as a sort of lubricant, a function that has been ascribed to the lipids normally excreted by the intestine (1). In addition, foods which contain or yield organic acids have been used.

The term laxative is so often used inadvisedly that it seems worth while to consider the meaning of the term. Sollmann (2) in his text on Pharmacology defines cathartics or evacuants as drugs which induce defecation either by (a) increasing the bulk (b) by preventing absorption of water, or (c) by causing irritation of the small or large intestine. Agar furnishes a typical example of the first group, salines of the next, and vegetable cathartics of the last. Sollmann describes laxatives as those substances which increase peristalsis moderately and produce more frequent stools of almost normal consistency without causing irritation. We agree with this description.

There are two general types of mechanical laxatives, (a) non-hygroscopic substances which act by softening the fecal mass thereby facilitating propulsion without definitely increasing the bulk (vaseline and liquid paraffin) and (b) hygroscopic substances which absorb water and expand considerably. Psyllium, agar and bassorin are representative of the second group. We have made a study of one of the substances in the latter group, namely, Karaya gum.

Nature of Karaya gum: Karaya gum is collected from the bark of a tree of the *Astragalus* species (*Stereuliaceae*). It is sometimes referred to as false or Indian tragacanth or *Stereulia* gum. It belongs to the general group of gums known as Bassorin gums. However, complete information regarding the chemical and physical properties of Karaya is not available in the literature. According to Pringsheim (3) the literature dealing with the gums and mucilages is very inaccurate and conflicting. Norman (4) states that no essential difference exists between gums and hemicelluloses; in both, hexose and pentose are linked with uronic acid. Solis-Cohen (5) gives arabin, bassorin and cerasin as the proximate principles of gums. Gums are chiefly pentosans. Many gums and vegetable mucilages, when dry, have the property of imbibing relatively large quantities of water. Porges (6), using a mucilage of the bassorin type, found that it imbibed about three times more water than linseed or psyllium seed, and five times as much as

agar. Parsons (7) and Klecker (8) reported that the bassorin they used absorbs slightly more than two times more water than agar.

We investigated the ability of Karaya to absorb water by comparing it with an equal quantity of agar. We found that when one gram of the Karaya† used in our study was added to 100 cc. of distilled water at room temperature (20° C.), it started to swell at once and within 20 to 30 minutes the beaker containing it could be inverted without spillage of the contents. Measurements showed that the Karaya gum will imbibe 96% of the water, and that an equal weight (1 gm.) of ground agar will imbibe 71% of the water. After 16 hours over sodium hydroxide in a vacuum desiccator, Karaya lost 13% of the imbibed water, and agar lost 54%. It is therefore evident that Karaya not only takes up more water than agar, but that it also holds it more firmly. It was these preliminary results that attracted our interest in Karaya as a bland substance which might be used to increase the bulk of the feces.

Fate of Karaya in the Gastro-Intestinal Canal. In view of the uncertainty as to whether hemicelluloses are digested in the gastro-intestinal tract, we deemed it advisable to determine whether Karaya is digested.

Feeding of measured amounts of unprocessed commercial Karaya gum (50-80 mesh) to ten dogs showed that the gum could be detected and most of it (95%) recovered from the feces by washing and selective filtration. The gum appeared as easily recognized masses of soft gelatinous composition for the most part separated from the fecal masses. All methods which we tried for the chemical isolation of the gum itself proved to be inaccurate.

Our efforts were then directed toward determining by chemical analyses of the dried feces whether any change in reducing substances occurred, and whether such a change might be used as an index of the disintegration of the gum in the intestine.

Six dogs were maintained on a standard diet and the stools were collected and analyzed for reducing substances. After a suitable control period Karaya was added to the diet for a five day test-period and then withdrawn for a second control period. The experiment was then repeated. It was found that the amount of reducing substances varied rather widely from day to day in both the control and test-periods. It was evident that if Karaya was disintegrated in the alimentary tract, it could not be detected by this method.

Williams and Olmsted (9) found such a very small quantity of copper reducing, sugar-like substances in the feces and such an abundance of volatile fatty acids that they decided to determine the volatile fatty acids quantitatively. They claim that the amount of the lower volatile

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†A special preparation of Karaya called Mucara and supplied to us by John Wyeth & Brother, Incorporated, manufacturing chemists, Philadelphia, was used.

fatty acids gives an indication of the degree of laxation, and believe that bacterial enzymes hydrolyze cellulose and hemicelluloses into soluble products which either are absorbed as such or are immediately fermented to gases and fatty acids, such as acetic and butyric acid which stimulate the gut. In their experiments, however, the volatile fatty acids were not increased during the feeding of pentosans. In our hands the determination of the volatile fatty acids by Olmsted's (10) method did not give results of sufficient value to warrant its use as an index of laxation in dogs receiving Karaya. However, this failure to demonstrate an increase confirms Olmsted's (11) finding that pentosans do not increase the volatile fatty acids. According to some investigators, the digestibility of pentosans depends on the combination in which they occur. This may explain some of the differences in the results reported in the literature (12).

We fed Karaya to two totally depancreatized dogs who were maintained on a standard diet and subminimal doses of insulin. Also, the starvation D:N ratio was determined on two phloridized dogs, after which they were given Karaya. In neither case was the sugar loss in the urine changed significantly and the nitrogen elimination was not influenced in the phloridized dogs. Tests for urinary pentose were negative in these and other experiments.

If Karaya gum is disintegrated at all in the alimentary tract of the dog, its disintegration is so slight that it cannot be detected by any of the usual procedures. Of course, it is possible that the gum may be broken down into products other than those for which we have tested. However, as previously noted, we were able to recover approximately 95% of the ingested gum in the feces.

Facilities were not at our command to enable us to maintain human subjects on controlled diets. For this reason we made no attempt to determine reducing substances or volatile fatty acids in their feces. The urine of ten subjects taking Karaya was analyzed for reducing substances and pentose but no change or increase was found.

Effect of Bacillus Welchii and Yeast on Karaya. Bacteria are known (12, 13, 14, 15) which can attack both free pentose sugars and pentosans, but the presence of microorganisms which are able to attack hemicelluloses in the human intestinal tract have not been recognized. Gossman (16) used Van der Reis technic and showed that cellulose-fermenting bacteria can be isolated from all parts of the small intestine of man during life. We decided to determine whether *B. Welchii* could split Karaya. Kendall (17) has shown that this organism will utilize sugar in preference to protein whenever possible. Sugar-free infusion broth was inoculated with a typical strain of *B. Welchii* and after 48 hours incubation at 37° C. the amount of copper-reducing substance was determined by the method of Peterson and Fred (18).

The results showed that the strain of *B. Welchii* used was unable to utilize the carbohydrate fraction of Karaya.

Concomitantly with these various studies, Karaya was being given to a number of human subjects (vide infra). A few of them remarked that Karaya seemed to cause flatulence. Since we had not yet demonstrated an appreciable breakdown of the gum in the gastro-intestinal tract, we were at a loss to explain the cause of the flatulence.

Another effort was made to demonstrate that Karaya could be attacked. A suspension of Fleischman's yeast was mixed with Karaya and incubated at 37° C. with adequate controls. After three days, fermentation was observed in all tubes containing yeast suspension and Karaya, but none occurred in the control tubes. This experiment was repeated a number of times and two additional series of tests

were made after the Karaya had been sterilized with alcohol to rid it of any possible contaminants. The results were not modified.

Although the results of all the experiments show that Karaya is fermented slightly after from 2 to 3 days incubation with Fleischman's yeast, the amount of fermentation was too slight to permit a collection and an identification of the gas formed (19).

The interpretation of all results obtained in studies concerned with the possible degradation of cellulose or of hemicellulose must be tempered by the thought that results obtained on animals or with normal human subjects does not necessarily hold under abnormal states such as constipation, or under conditions of dietary peculiarities. Cowgill and Sullivan (20) suggested that the intestinal flora of the constipated individual might be peculiarly capable of decomposing plant roughage to a high degree. Cowgill and Anderson (21) found that the daily amount of roughage required to cause laxation was approximately 40 mg. per kg. of body weight greater in the individual with simple constipation than it was in the normal person.

Effect of Karaya on Nitrogen Utilization. Bastedo (22) quotes Whiteacre (23) as proving that bassorin paste reduces the assimilation of protein. An increase in the nitrogen in the stools on adding indigestible residue to the diet of animals and man has been observed by others (24-27). It has been shown by several investigators (28-31) that the fecal nitrogen is more closely related to the total bulk of the food consumed than its nitrogen content. Such effects have been attributed chiefly to the increased intestinal passage time, which decreases the assimilation of protein, but the amount of epithelium cast-off and a change in the flora must also be in part concerned.

The effect of indigestible residue on nitrogen excretion seemed quite important, since it is possible that Karaya might be taken consistently for long periods of time by some persons, particularly elderly persons with a simple type of constipation. Ten grams of Karaya were fed daily to five dogs for three months and no ill effects upon maintenance of weight or nutrition were observed. Then, metabolic studies were performed on five dogs in which the fecal nitrogen loss was determined before and after giving ten grams of Karaya with a basal diet of meat.

PROCEDURE

Five dogs were placed on a basal diet of 500 grams daily of whole ground beef heart. For three of the animals all feces were collected, weighed and then dried to a constant weight, for a five day period. A five day control period on beef heart alone was followed by a similar period during which 10 grams of Karaya were added to the diet. Carmine was used as a marker. Two of the animals were on the same regime but with the addition that a second control period followed withdrawal of the Karaya. The nitrogen of 500 mgm. samples was determined by the standard macro-Kjeldahl technic. No nitrogen could be found in the Karaya we used.

RESULTS

Dogs I and V showed an increase in nitrogen excretion while on Karaya of 38.4% and 35.7% respectively. Dogs II and IV showed decreases of 11% and 30% respectively. Dog III excreted the same amount of nitrogen on Karaya as during the control period. In two dogs feces were again collected after withdrawal of Karaya. An interval of three days was allowed to elapse between feeding of Karaya and the beginning of this last period of stool collection, in the

hope that all the Karaya would have been evacuated by that time. One of these animals excreted 50% more nitrogen than he did during the first control period and 10.5% more nitrogen than during the feeding of Karaya. Dog IV excreted 30% less nitrogen on Karaya than before it was given, but excreted 16.2% more nitrogen during the test period following Karaya than while taking Karaya.

Summarizing, the nitrogen excretion was unaffected by the addition of Karaya to the diet in one dog, the excretion was increased in two dogs and decreased in two dogs. Following the feeding of unprocessed commercial Karaya gum, nitrogen excretion was still further increased in one animal and decreased in another for a five day period. These results justify the conclusion that the bulk provided by 10 grams of the gum, Karaya, causes a variable effect on nitrogen excretion by way of the feces.

An increase in fecal nitrogen excretion would be anticipated if the passage of food through the gut were so rapid as to interfere with the assimilation of the protein in the diet. By using the carmine marker method, Karaya in 10 gram doses did not show a marked increase in their peristaltic rate in five dogs. However, the average number of defecations increased 60% with crude Karaya, and 53.9% of the human subjects (vide infra) had an increased number of stools. This seems to indicate that the time of passage through the alimentary tract is not increased, but the laxation rate, as defined by Cowgill and Anderson (21), is increased.

Our studies on 6 dogs with Mucara* containing Rhamnus Purshiana showed that passage through the alimentary tract is accelerated by from 4-8 hours. Rhamnus Purshiana belongs to the class of emodin cathartics which are known to increase the peristaltic movements of the colon, therefore, this acceleration was not unexpected.

It is our belief that bulk provided by Karaya may under some conditions influence food nitrogen assimilation, but that the amount which would be used for therapeutic purposes probably would not provide bulk of sufficient magnitude to interfere significantly with this important metabolic activity.

Effect of Karaya on Starch Digestion in the Dog.

Procedures: Six normal dogs were placed on the high starch diet used by Beazell, Schmidt and Ivy (32) which consists of 62% starch, 21% protein, 17% fat and 2 cc. of cod liver oil daily. One Kilogram of this diet was fed for several days, then all feces were collected for a five day period both before and while feeding 10 gm. of Karaya daily. Representative samples were analyzed for starch by the method devised by the above authors. Our technique varied only in that the feces were not washed with alcohol and ether to remove certain of the non-sugar reducing substances. This made our values somewhat high throughout the series, but since our interest lay in determining whether there was any interference with the digestion of starch when Karaya was given, the high values, per se, were not of concern to us.

The results show that with a high starch diet an increase in the amount of reducing substances (determined as starch) in the feces occurs on feeding Karaya, yet the increase is so small as to be practically negligible. Yet, the increased rate of passage of starch through the intestine may explain the increase in flatulence reported by a few of the human subjects. The lack of ptyalin in the saliva of the dog necessitates that all starch be digested in the intestine; therefore,

*This is the trade name under which the Karaya we used is marketed.

even such a slight increase in the intestinal peristaltic rate as might occur on the addition of Karaya might be just sufficient to pass the food through the small intestine before the enzymes could completely attack the starch.

Effect of Karaya on Vitamin A Utilization. A series of rat experiments were conducted to determine whether Karaya exerted a deleterious effect upon vitamin A utilization.

Procedure: Group I. Twenty-nine female albino rats 18-21 days old were placed on a basic vitamin-free diet supplemented with four drops of cod liver oil and 400 mg. of Brewer's yeast (vitamin A free) daily. As soon as consistent weight gains were recorded twenty-seven rats were started on a deficiency regime by substituting viosterol for the cod liver oil. The two remaining rats were maintained as controls. At the beginning of the observation period the average weight of the entire series was 27 grams, and the average weight at the start of the deficiency regime was 52 grams, or an average gain of 3 grams per day. As deficiency appeared alternate animals were placed in Groups A and B. Our criteria for vitamin A deficiency were ophthalmia and declining weight. However, we placed more reliance upon the appearance of ophthalmia for it had been our experience in a previous study in which the weight curve was taken as the sole criterion that many animals reached such an extreme degree of avitaminosis that it was impossible to bring them back to a healthy state. Steenbach and Coward (33) used the incidence of ophthalmia as an index of vitamin A deficiency.

The diet of Group A animals was supplemented with one gram of Karaya daily (provided as pills mixed with dextrin) and four drops of cod liver oil, and the rate of return to a healthy state was recorded. The animals in Group B were on the same regime as the animals in Group A except that no Karaya was given.

An average difference of only 4 days occurred in the time required to observe deficiency signs in the group receiving and the group not receiving Karaya. The time required for recovery from vitamin deficiency was also quite close in the two groups (Group A—17.6 days; Group B—19.8 days). No other differences were noted between the groups. Examination of the intestine of twelve of the rats (6 of which had been fed Karaya and 6 had not) exhibited no gross differences or abnormalities at the end of the experiment which lasted ninety-one days.

Group II. Seventeen female albino rats of an average weight of 33 grams were separated into Groups II (a) and II (b) consisting of nine control and eight test animals respectively. These animals were fed a standard diet complete in all respects. The diet of Group II (b) was supplemented with one gram of Karaya daily. All animals were weighed and observed twice weekly for sixty days.

The nine control animals gained an average of 181 grams each and the eight test animals fed Karaya gained an average of 183 grams. All maintained normal healthy coats.

It appears from the results of these experiments that relatively large amounts of Karaya fed continuously to young albino rats neither interferes with their normal growth, nor delays or prevents recovery from an induced vitamin A deficiency.

Effect of Karaya on the Feces of Normal Dogs. Since we were primarily interested in the value of Karaya as a laxative substance, we determined whether it was a truly bland material which would only increase the bulk and moisture content of the feces, and increase the number of stools either by distending the bowel or

by chemical stimulation. The literature contains no note regarding its possible irritant qualities; in fact there is no literature bearing on the medicinal use of Karaya.

Experimental procedure: Eight normal dogs were maintained on an adequate basal diet which caused an average of one normal defecation daily. The animals were fed daily at 8 a. m. Large water jars were kept in the cages. Total feces were collected for five-day periods, care being taken to avoid drying before the weight could be ascertained. The total output was weighed then dried in a hot air oven at 90-100° C. and reweighed as soon as a constant weight was reached. The difference between the first and the final weights was taken to represent the moisture content. Following a control period 5 grams of unprocessed commercial Karaya gum previously swelled in 100 cc. of distilled water were added to the daily diet for seven days. This was followed by three days of basal diet again, then seven days with test material added to the diet. The last five days of this period represented the actual test period. This procedure of three days between the control and test periods was followed throughout the study. The observations recorded upon the daily feces were (1) number of defecations, (2) character, (3) total weight, (4) final weight, (5) moisture (obtained by calculation).

Number of Defecations: The average normal daily number of defecations was one. Feeding 5 grams of unprocessed Karaya daily caused the average to increase to 1.6 (extremes 1-2.4); Mucara caused an increase to 2.2; Mucara with cascara produced an average of 1.6 (extremes 1.4-2.0); Mucilose raised the number to 1.4 (extremes 1.0-2.0).

Character of the Feces: In all dogs unprocessed Karaya caused the feces to soften, but rarely produced other than a poorly formed stool. Mucara softened the stools considerably more and not infrequently produced a formless mass. Mucara prepared with cascara showed approximately the same changes with the exception that there was possibly less tendency toward a formed stool. Mucilose also softened the stool, but it made the feces so gummy that the particles of feces adhered firmly to the weighing dishes. Agar caused some softening but definitely less than the other substances studied.

Total Bulk: The changes which occurred in the total bulk of the feces during the various test periods is interesting. Mucara increased the bulk most with an average for all dogs of 164.55%; Mucara with Cascara was next with an increase of 88.16%; Agar with an increase of 58.06%; Karaya with an increase of 52.25%; Mucilose with an increase of 48.93%.

These values assume more interest when compared with the changes in moisture content. Mucara caused an increase, average for all dogs, of 184.85%; Mucara with cascara increase of 101.85%; Karaya increase of 64.23%; Mucilose increase of 54.11%; Agar increase of 43.15%.

The variations observed in the order of values cannot be explained by the evidence at hand. Many factors should be considered, such as the effect of the substances on bacterial flora, excretion of lipids by the gut, their effect on absorption, their particle size, the water imbibed and their degradation in the alimentary canal.

Finally, an attempt was made to determine whether Karaya fed over a long period of time was irritating or lost its effect. After the usual control period of five days three dogs were fed unprocessed Karaya for thirty consecutive days. The stools were collected for

the five days immediately after termination of the feeding of Karaya. In all dogs the average daily grams of bulk were increased as was also the daily moisture content. The proportion of moisture to bulk also increased in all three dogs. Three weeks after discontinuing Karaya another control collection was made. Two of the three dogs had virtually returned to the original level. The values for the third dog had decreased from those obtained immediately after the Karaya but had not reached the original control level. This suggests that the action of Karaya might persist for a short time after discontinuance of the dose.

Cowgill and Anderson (21) found that normal men who changed suddenly from a high level of fiber intake to a low one showed a "hang-over" effect for several days. It seems that this increase following the feeding of Karaya must be other than a hang-over from the bulk provided by Karaya since the time elapsed (three weeks in 3 dogs) was long and the diet of the animals had been shown to be bulky enough to produce a daily stool, thereby excluding the lagging behind of the gum. This "after effect" will be discussed later under the human studies.

EFFECT OF KARAYA ON HUMAN SUBJECTS

Karaya was administered in the form of granules under the trade name of "Mucara," to 89 graduate and medical students, nurses and social workers (46 were female; 43 were male). Each subject kept an accurate account of all food and fluids taken for seven days. This diet was then repeated on the same days of the following week with the addition of one heaping teaspoonful of Mucara taken once daily after the evening meal (9 gms. Mucara = approximately 7 gm. Karaya). All stools were collected for the first five days of the first week and analyzed for bulk, moisture and character to provide a control period. The Mucara was started on the sixth day and was taken daily for four weeks. Stools were collected again on the 8th, 9th, 10th, 11th and 12th days to represent the test period. In a few instances where no effect from Mucara was noticed during the test period stools were again collected during the last five days of the month during which the Mucara was taken. Subjects were instructed to note any subjective sensations which developed while taking Mucara, but were given no idea as to any specific information which would be desired later.

The criteria upon which we based our opinion as to whether the desired laxative action was obtained concurred in the main with those laid down by Cowgill and Anderson (21) namely: (1) The subjective impressions of the person as to completeness and satisfactory character of the defecation. (2) The amount of intestinal contents evacuated under test conditions. (3) Water content of the stools. (4) Time of passage of material through the alimentary tract. (5) Number of defecations in a unit of time (laxation rate). (6) Amount of indigestible matter in the stool and the relation of this to the quantity ingested. The voluminous data obtained cannot be given in detail hence where ever possible the figures have been averaged or condensed so as to give the clearest picture of the changes which were apparent.

Sixty-six or 74.1% of the 89 subjects whose stools were analyzed reported the existence of a normal habit. For the sake of uniformity we have interpreted this to mean an average of about one stool daily from week to week, (in a few instances this would mean one stool

every third or fourth day). A few of the subjects reported 2 to 3 stools daily, but if this were their customary habit over long periods of time, and if the stools were soft, not excessively dry, well formed, and not preceded by, nor accompanied by discomfort, and there were none of those symptoms so frequently attributed to "autointoxication," we considered the individual to have a normal habit. Twenty-three or 25.8% reported constipation as their usual state. We interpreted this as marked irregularities of habit, poorly formed fecal masses, often scybalous, inspissated, accompanied by straining and discomfort and those symptoms so often attributed to "autointoxication." Many of these constipated individuals considered it necessary to use enemas or cathartic drugs frequently. Most of them had consulted physicians for constipation.

Bulk Production: Thirty-six or 40.4% of the total of 89 subjects reported that they were aware of an increase in the bulk of the stools while taking Mucara. This is interesting when one considers that by actual weight of the stools we found that 72 of the 89 (81%) showed an increase in bulk during the first five days on Mucara which ranged from a minimum increase for the five days of 15 grams or 2.4% up to 922 grams or 293.6%. Two other persons, who had a decreased bulk during the first five days, showed an increase during the last five days of the month. Eight subjects showed a decrease in bulk for the first five days on Mucara which ranged from 14 grams or 4.2% to 426 grams or 77%. Seven of these had an increase in bulk when they took Mucara with cascara.

Fifty-seven or 86.3% of the 66 individuals with normal habit obtained an increase in bulk and/or moisture with plain Mucara. Five or 7.6% of those with normal habit showed a decrease in bulk and moisture.

Fifteen of the twenty-three constipated subjects showed an increase in bulk and/or moisture with Mucara. Surprisingly, eight of these had a decreased bulk and moisture. Subjectively, the constipation was relieved in nineteen of the twenty-three subjects who reported constipation.

Moisture Changes: Sixty-seven or 75.2% of the total subjects reported increased softness of the stools while taking Mucara. Actually 75 or 84.2% exhibited increase in moisture during the first five days on Mucara. The increases ranged from 29 grams or 1.2% to 517 grams or 267%. One subject showed an increase in moisture only during the last 5 days of the experimental test period.

Eight of the total, during the first five days, showed a minimum moisture decrease of 18 grams (4.7%), to a maximum decrease of 374 grams (67.9%). Five of these acquired increased moisture when the cascara mixture was given in place of plain Mucara.

Number of Defecations: Forty-eight or 53.9% of the total showed an increase in the number of stools passed over a five day period. Twenty-eight increased by 1; 12 by 2; 4 by 3, and 4 by 4 stools. Only 12 or 13.4% of the total subjects were aware of any change in the number of stools passed over the control period; the records gave the actual increase. Fourteen or 15.7% of the total had a decreased number of stools. Eight were decreased by 1; 3 by 2; 2 by 3, and 1 by 4 during the five day period.

Subjective Impressions: Thirty-eight or 42.7% had increased consciousness of the call to defecate. Twenty or 22.4% claimed that Mucara produced a more satis-

factory and complete defecation. Six or 6.7% were less satisfied because of the soft character of the stools. Two or 2.4% remarked that the stools were firmer and drier and more difficult of passage. (Both actually had a decreased bulk and moisture). Seven or 7.8% complained of some abdominal discomfort associated with distension shortly after taking Mucara. Three or 3.4% complained of mild abdominal cramps while taking the Mucara. One subject complained that by the end of the third week on Mucara the stools were so soft as to be irritating on passage. Six or 6.7% reported that they were thirsty as long as they took Mucara daily. Four or 4.7% reported that the constipation which they customarily had in relation to the menstrual period was absent while taking Mucara regularly. Ten or 11.2% remarked on the malodor of the stools. Thirteen or 14.5% reported that the laxative effect of Mucara lasted for from 36 hours to several days (one reported several weeks) after it was no longer taken. Four or 4.5% reported either no stools or hard stools for from one to three days after stopping Mucara. One subject had a decreased urge to defecate for 10 days after starting Mucara (bulk and moisture were both decreased in this subject). One subject reported that his *Acne Vulgaris* disappeared while he was taking Mucara daily and that it returned within one week after stopping. No previous dermatologic or dietary therapy of any type had ever influenced his *Acne*, even yeast! One subject required mineral oil frequently because of painful hemorrhoids; occasional doses of Mucara replaced the need for mineral oil.

Flatulence: Fifteen or 22.7% of the sixty-six with normal habit were not aware of flatulence before this experiment but developed it while taking the Mucara. Twenty-one or 31.8% usually had flatulence and also had it while on the Mucara. Nine of these thought there was an increase in the degree of flatulence; 10 had less and 2 thought it remained about the same. Thirty-two or 48.2% of those with normal habit either had no flatulence before or after starting Mucara or else noted no change from their customary state. Twenty-two or 23.6% of the 89 subjects became aware of flatulence while taking Mucara whereas they considered themselves free of it before.

MUCARA WITH CASCARA

Nine individuals who failed to respond to plain Mucara were studied, with the same dose of Mucara with cascara. Four of these acquired an increased number of stools; 1 by 1; 1 by 2, and 2 by 3. Seven had an increase in bulk and moisture; one of these experienced drastic purging with this preparation. One had decreased bulk but increased moisture and 1 showed a decrease in both bulk and moisture.

SPECIAL EXPERIMENTAL SUBJECTS

Twelve patients were given Mucara without an analysis of the stools being made. The tabulation which follows is self-explanatory:

Two subjects not studied quantitatively received no relief from their constipation with plain Mucara, but were kept comfortable by a daily dose of Mucara containing cascara. One subject was aware of no change when the cascara mixture was substituted for the plain Mucara. One subject who had partial ileocecal obstruction due to adhesions remained entirely free from constipation as long as she took one daily dose of plain Mucara. One subject who "needed" enemas every third day in order to have a

bowel movement obtained no relief with either plain, or Mucara with cascara. One subject with duodenal ulcer who has taken Mucilose regularly, prefers Mucara with cascara, but she obtained no relief from the plain Mucara. Six subjects with simple constipation who asked to try Mucara have come back repeatedly for more. Previous medication of various types which they used were never as satisfactory as Mucara, they reported.

DISCUSSION

The discussion will be limited to those factors which are most concerned with the laxative properties of Karaya. The criteria upon which this evaluation is made have been previously referred to. In this connection the important work of Olmsted and Williams (15) should be mentioned. They based their evaluation upon two criteria: (a) the impressions of the subject as to whether or not the bowel movements were satisfactory, (b) the weight of the feces over and above the weight of the residue recovered in the feces. Due to our inability to feed our subjects quantitatively prepared diets, we were unable to determine the residue values for the diets.

The majority of our subjects reported a normal bowel habit. We were glad that this partition happened to occur for we knew from preliminary tests that Karaya was of value in constipation, but we had no knowledge of other properties it might possess. The use of Karaya by a group of normal persons should readily divulge any peculiarities of the substance.

An increase in bulk was the most consistent change noted in the experimental subjects. Williams and Olmsted (15) have shown that the hemicelluloses are more efficacious in increasing the bulk of the stool than are the cellulose or lignin fractions of indigestible residues. This effect of hemicellulose is amply demonstrated by our studies with Karaya. We found that the effect on bulk was proportional to the moisture in the majority of the subjects. The increase in bulk and moisture bore no relation to the quantity of bulk fed nor to the amount of water which could be absorbed by the given amount of gum, therefore, some less direct factor must also be concerned in the production of bulk. Whether this is due to a simple washing down of less fully digested food particles, protein for example, or whether due to increased glandular activity with resultant increase in cast off solids, we are unable to say.

The conditioning of the defecation reflex which occurs in so many human beings prevents the use of the record of the number of defecations per unit of time as an accurate criterion of laxation in Man. Over half of our human subjects gave evidence of an increase in the number of stools which we consider of definite significance in view of the fact that the same preparation more than doubled the number of defecations in the dogs under experimental conditions.

Although slightly less than half of the subjects had an increased urge to defecate, none of them reported this an undesirable feature. Hines, Lueth and Ivy (34) have demonstrated the marked variability in sensitivity to pressure within the rectum among human beings so that quantitative figures cannot be considered highly important on this point. It is worth mentioning that the increased urge did not appear to be caused by irritation other than that produced by distension, although here again proof is difficult.

About one-fourth of the subjects volunteered that Mucara produced a more completely satisfying defeca-

tion. When directly questioned on this point many others readily admitted that this was also their experience. We did not wish to include answers that were influenced, therefore we did not add these to the reports voluntarily made.

We see no adequate reason why the six subjects should have noticed increased thirst while taking Mucara. Two of these admitted that customarily they drank less than three glasses of fluids daily. One of the subjects drank six glasses daily at our request and reported that as long as she remembered to take that amount of fluid she was not thirsty and the stools were softer.

The failure to defecate for a few days after withdrawal of Mucara which occurred in four can be readily explained on the basis of sudden reduction in bulk.

The complaint of abdominal discomfort and mild cramps which occurred in a few subjects shortly after taking the Mucara is difficult to explain. How large a part psychic reaction plays when one knows that he has ingested a substance which swells we do not know. Tost (35) claimed that bassorin swells only very slightly in acid gastric juice. We added one-half gram of Karaya to 10 cc. of acid fasting gastric juice and found that it swelled to about the same extent as did one-half gram of Karaya in distilled water, but that the rate at which the Karaya swelled in gastric juice was about half that in the water. The recent report (36) of esophageal obstruction from another type of hygroscopic laxative should be borne in mind only if extremely large doses are given. The small size of the Karaya particles used in preparing Mucara tends to eliminate any such sudden swelling as may occur with differently processed material.

The malodor of the stools reported by some of the subjects might be associated with the liberation of certain gases if degradation of the gum occurs. We observed the feces particularly for gross evidence of fermentation because Bastedo and others have reported that bassorin stools are fermentative. It is thought that the fermentative stool might be due to the fact that the gums carry down undigested food.

Williams and Olmsted (15) state that the passage of flatus is as normal as the passage of feces, for the carbon dioxide and hydrogen passed are the normal excretory products of bacterial fermentation. In our interviews with subjects it was almost impossible to obtain accurate evaluation of the facts for when pressed, nearly all acknowledged the passage of occasional flatus which they themselves considered normal. We tried to base our data, therefore, on any symptomatic change in the degree of flatulence but here again the focusing of the attention on a symptom made it difficult to draw conclusions. We believe that there was a definite tendency toward increased flatulence on Mucara in 24.7 per cent of the subjects. However, with very few exceptions those who reported the greatest degree of flatulence remarked that it was never so annoying as to cause them to wish to discontinue the experiment.

The "after effect" of bulk has been partially discussed in the section on studies on the dog. From our clinical observations we believe that while part of the effect might result from the retention of gum in the gastro-intestinal tract, another factor is important. That is, the tendency for the individual to pay more attention to his habit, and the greater ease with which

a normal habit can be established when the stool is soft and bulky. Many of our subjects remarked that while taking Mucara the urge to defecate was more likely to come at their ordinary "stool time." We believe that one of the most important factors in the causation of constipation is the lack of a strong urge at the time of the day when defecation is most physiologic, namely, after breakfast. If the bulk is sufficient to initiate a definite urge, and the stool is soft and easy of passage one is more apt to heed the "call." It is largely because of this ability of Karaya to provide bland bulk and moisture that we consider the gum a valuable adjunct for the management of simple constipation.

The failure to increase the bulk and moisture of eight constipated subjects might be due to the peculiar situation described by Cowgill and Anderson (21) when they found that the roughage requirement of the constipated person was definitely in excess of the non-constipated. Further study is needed to clarify this observation.

The "hang-over" effect of Mucara has an important clinical application. We found that a few of the constipated patients studied had to take Mucara daily at first in order to achieve a regular, soft and satisfactory stool, but that as soon as this was established they were able to maintain it by taking the same dose of Mucara every second, third or fourth day. In fact, three previously constipated subjects who have continued to take Mucara of their own accord have found that they were able to take the doses an increasing number of days apart until finally a single dose of Mucara about once a week would maintain a normal habit.

Our studies with Mucara containing cascara were

brief and performed only on those persons who were unaffected by the plain compound. Its usefulness seems limited to such patients.

SUMMARY AND CONCLUSIONS

Karaya gum will absorb and hold a large quantity of water.

Karaya is not attacked by *B. Welehi* in vitro, but is slightly fermented by yeast.

Experimental evidence fails to prove that Karaya is appreciably disintegrated in the alimentary tract, for feeding Karaya to dogs does not increase the copper-reducing substances in the feces; does not increase the sugar excreted by depancreatized dogs; does not effect the D:N ratio in phloridzin diabetes. It does tend to increase fecal nitrogen excretion, although the effect is variable; it does not appreciably affect starch digestion in dogs receiving an excessively high starch diet; and does not inhibit the utilization of vitamin A in rats.

Karaya, in its unprocessed form, as well as in its processed form, Mucara, causes changes in the feces of dogs, such as increased number of defecations, increased bulk and moisture, and does not cause detectable irritation.

Mucara has been proved to be a useful, harmless laxative agent because it increased the bulk of the stool in 80.8 per cent of the human subjects studied; increased the moisture content in 75.2 per cent; increased the number of defecations in 53.9 per cent; and increased the urge to defecate in 42.7 per cent. It relieved constipation in 19 of 23 persons studied.

Mucara produces no harmful effects, nor is it habit-forming if taken over long periods of time. The evidence suggests its value as a regulator of bowel habit.

Mucara with added cascara is useful in those subjects who fail to respond to plain Mucara.

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Intussusception in the Adult*

By

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INTUSSUSCEPTION is essentially an accident occurring most frequently during infancy and early childhood. Its recognition dates back many centuries. Hippocrates suggested treating the obstruction by inflation of the bowel from below (1). The first real descriptions of the condition were made by the anatomists of the 16th century who, however, associated it with volvulus from which it was separated by Peyer in 1677 (2). The first clinical observations were made during the 18th century notably by Kuhn in 1702, Velse in 1742, Hevin in 1768 and by John Hunter in 1789. The latter defined intussusception as "the passing of one part of the intestine into the other and commonly by the upper passing into the lower" (1). This almost 150 year old definition holds good today.

Meckel, Rokitsky and Cruveilhier reported cases with their treatment. It is not, however, until 1871 that we find the first record of abdominal section for intussusception by Mr. Jonathan Hutchinson (1). A review of the literature for the past 50 years reveals innumerable studies on intussusception mostly, however, in children under two years of age. Perrin and Lindsay (3) in a study of 400 cases found 78.5 per cent occurred in children under two years of age and only 4.5 per cent in patients over 14 years of age. According to Hinton (4) 95 per cent of all acute intussusceptions occur in children. Sullivan (5) and Dieulafoy (6) both stated that it is almost the only cause of obstruction in infants.

Lutzow and Holm (7) commented on the fact that intussusception is uncommon in Norway, only 29 cases having been recorded up to 1923. On the other hand it is quite common in England and Denmark. This is possibly due to the extensive use of calomel and castor oil in children in the latter countries.

Intussusception may be acute or chronic. The acute form is almost always found in children while in adults the chronic form is by far the more common. However, Mayo and Philip (8) in a study of 39 patients suffering from chronic intussusception reported one instance in a patient only ten years of age. Schlink also reported one case of intussusception lasting two months in a female child seven years of age, with recovery after operation. Elliot and Corscaden (9) in a very exhaustive study collected 300 cases from literature. They found that in St. Thomas Hospital, London, from 1875 to 1900 only 115 instances of intussusception were reported, of these only 10 per cent were in adults over 15 years of age. They also quoted Codman's report of 27 cases from the Massachusetts General Hospital prior to 1908 with only nine instances in adults. Davis (10) studied the records of St. Luke's and St. Mary's Hospitals in Duluth, Minnesota, and found that out of 113,351 patients admitted, intussusception was found in only 22 instances. This is at

the rate of one case of intussusception to about 5,000 admissions. Of these, only one patient was an adult 34 years of age.

In the Beth-El Hospital, 62,632 patients were admitted during the past 11 years with only six instances of intussusception, only one was an adult, our own case.

Invagination may occur in any portion of the bowel and true to Hunter's definition it is usually the upper segment that passes into the lower segment. Nevertheless, a number of instances of so called retrograde intussusception have been reported. In this condition the lower segment passes into the upper one.

The most common site for retrograde intussusception appears to be the gastro-enterostomy opening, where more or less of the jejunum is invaginated into the stomach. Becker (11) collected 38 cases from the literature, 23 females and 15 males, the youngest was 21 and the oldest 75 years of age. According to Sibley (12) the mortality of patients with retrograde intussusception appears to be high, about 50 per cent. The operative mortality was about 40 per cent but of those patients who were operated within 48 hours only 10

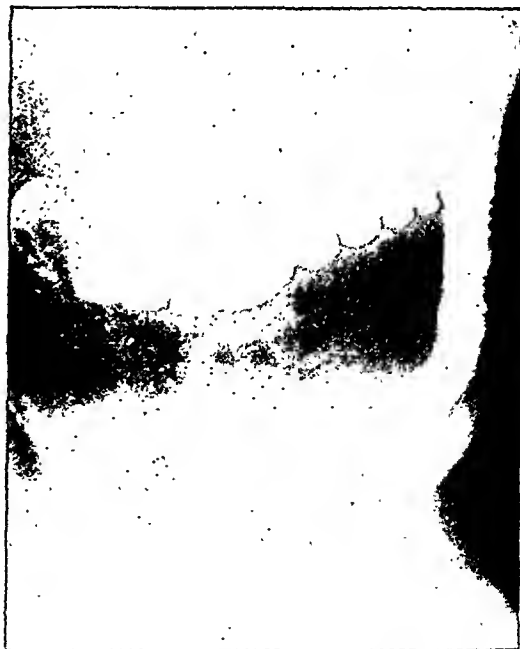


Fig. 1. Showing transverse and descending portions of the colon with a tumor mass occupying the transverse portion, spasm in the presplenic region and absence of ascending portion of the colon.

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Submitted November 17, 1937.

per cent died. Four patients who were not operated upon died.

Lewis (13) reported one case of retrograde intussusception in which the apex was the pelvic colon which was intussuscepted through the transverse and ascending portions of the colon reaching the cecum. Balfour (14) reported an instance of retrograde intussusception of the sigmoid due to tumors within the bowel with powerful antiperistaltic contractions in the proximal sigmoid. Intussusception may also occur during pregnancy. Chaffin (15) collected 11 cases from the literature since 1870.

As a rule only a single intussusception occurs. Although after reduction it may recur at the same site if not operated upon or at another site as reported by Blaxland (16). Multiple intussusceptions are rarely found in life but a number have been reported on post mortem examinations especially in the small intestine. They are probably caused by increased intestinal peristalsis during death agony (17).

The direct cause of intussusception is still not very well understood. Elliot and Corsecaden in their study found 33 1/3 per cent caused by tumors within the bowel; 60 per cent of these tumors were of a benign type and mostly found in the small intestine; 40 per cent were of a malignant variety and usually found in the large bowel especially in the proximal colon. Tumors found in the sigmoid and rectum were usually of a benign character. In 1936 Christopher (18) gathered from literature 43 more cases of intussusception due to benign tumors and 16 cases due to malignant tumors. Other causes are Meckel's diverticulum, the appendix and various forms of intestinal ulcers. An interesting case of intussusception in a



Fig. 3. Showing the transverse and descending portion of the colon filled with air and the tumor mass being pushed backward by the air pressure with attempted reduction of the intussusception.

patient suffering from ulcerative colitis was recently reported by Barger (19). Intussusceptions of the appendix alone have been reported (20).

The mechanics of intussusception consists of the telescoping of one portion of the tube into another. Where a malignant tumor or deep ulceration is present the adjacent intestinal wall becomes stiffened and the lumen narrowed. Peristaltic waves approaching this area are unable to pass through this stiffened segment but carry it forward into the distal bowel. Once an invagination has taken place peristaltic action pushes the intussusception forward as far as its attached mesentery will permit. In case of a polyp the mechanism appears to be somewhat different. The peristaltic wave pushes the polyp forward as it would any foreign body. Through its attached pedicle the polyp drags along the wall of the intestine and here also when the invagination takes place further intestinal peristalsis pushes the head forward. Where no polyps or tumors exist it is difficult to assign a definite reason for the intussusception. In such cases sudden hyperactivity in an intestine with an abnormally long mesentery or a defect in its wall has been considered the most likely cause.

Four types of intussusception have been described. 1. Ileocecal; the ileocecal valve and the adjacent ileum pass into the cecum and colon. 2. Ileocolic; the ileum alone prolapses through the ileocecal valve into the colon. 3. Colic; the large bowel is prolapsed into itself. 4. Enteric or ileal; the small bowel alone is involved.

The treatment is usually surgical. If seen and diagnosed very early, especially in children, attempts at reduction may be made by repeated enemas. Usually when the patient is seen by the physician adhesions have already formed, inflammation and edema are



Fig. 2. Showing the transverse and descending portions of the colon contrasted with air which outlines the tumor mass within the transverse colon.



Fig. 4. Showing the result of final operation with continuity of the ileum and transverse portion of the colon.

present and only through surgery is reduction possible. Because so many intussusceptions are due to tumors or polyps resection of the mass is the usual procedure.

REPORT OF CASE

The patient (Case No. 75748), a male, age 33 years, was admitted to the Beth-El Hospital February 12, 1936. He had been in good health until about six months previously when he noticed that he became dyspneic on exertion. At the same time he was disturbed by intermittent cramp like pains which radiated toward the back and both sides, usually accompanied by borborygmus and passing of flatus which seemed to relieve the cramps for the moment—the history of a partial intermittent obstruction. The cramp like pains appeared at irregular intervals and lasted from five to fifteen seconds. These symptoms increased in frequency until at the time of admission to the hospital they occurred almost every five minutes without any relation to meals. Alkalies and food seemed to have no effect on the symptoms. During the month before admission the patient had two or three loose bowel movements per day instead of the single normal bowel movement before the onset of the present condition. At times the loose bowel movements were tinged with blood. During the six months of illness the patient lost about thirty pounds in weight.

Because of his dyspnea and general weakness the patient consulted a physician who found nothing abnormal on physical examination, but a blood count revealed that the hemoglobin was only 40 per cent. A few months of treatment raised it to 60 per cent at which level it persisted until he was admitted to the hospital.

On admission, examination of the heart and lungs revealed no abnormal findings. Examination of the abdomen revealed a soft, elongated mass above the umbilicus quite tender and extending across the midline.

Laboratory Examinations: The urine showed no pathological changes with the exception of a few coarsely granular casts. Gastric Analysis disclosed a low acid value. The stool at the time of the examination showed no occult or gross blood.

Blood Count: Hemoglobin—60 per cent; RBC—4,400,000; WBC—18,350; polymorphonuclear—75 per cent; lymphocyte—23 per cent; monocyte—2 per cent.

X-ray of the Colon: Under the fluoroscope the opaque fluid flowed in freely from the rectum to the pre-splenic flexure region where a definite delay was noted lasting a few minutes due to spasm. After overcoming the spasm, the transverse colon filled rapidly, the flow stopping at the hepatic flexure which could not be visualized. Under the fluoroscope, the transverse colon was felt as a large, elongated, soft mass tender to palpation. The roentgenogram showed a dilated transverse colon fusiform in shape with an apparent contraction in the pre-splenic flexure region (Fig. 1). In the region of the hepatic flexure there was an irregular and defective filling. After evacuation, air was injected, another roentgenogram was taken which revealed a dilated proximal transverse colon with the outline of a tumor mass within the lumen of the dilated portion of the transverse colon (Fig. 2). Further distending the colon shows an attempt at reduction of the intussusception (Fig. 3).

Surgical Report by Dr. A. Iason: The abdomen was opened through an upper left rectus incision. A large mass was noted showing evidence of sub-acute and chronic inflammation which involved most of the transverse colon. On further inspection the cecum and appendix were found to be missing, and tracing the ileum it was found that the lower ileum, cecum and ascending colon were intussuscepted into the transverse colon as far as the splenic flexure. The intussusciptiens had lost part of its luster and showed a marked hypertrophy. The apex of the intussusceptum, at about the splenic flexure, on palpation, gave the impression of a mass. There was edema and congestion of the mesentery of the transverse colon and a small amount of fluid present in the abdominal cavity.

The mass was reduced by careful pressure on the intussusciptiens distal to the head or apex of the intussusceptum, thereby forcing the entire intussusceptum out. Because of the induration and apparent lack of viability of the cecum and ascending colon, it was deemed advisable to remove this portion of bowel, including the lower ileum. This was accomplished by a multiple-stage procedure. The lower six inches of ileum and the entire ascending colon were

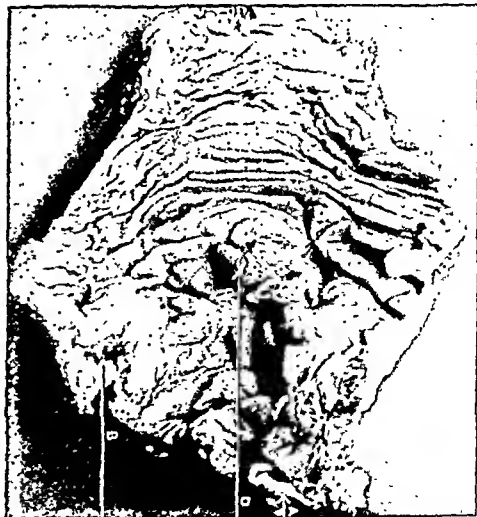


Fig. 5. Photograph of resected cecum and portion of ascending colon. At A is the appendiceal opening; at B the ileo-cecal valve (transposed in opening the specimen); at C the distal end of the cecum; and at D the tumor mass.

brought out into the wound in the manner of a Mikulicz operation.

About four days later the exteriorized bowel was removed. Ten days after that a spur clamp was applied, obliterating the wall between the limbs of the bowel. The patient's recovery was uneventful and he was discharged in the fourth week with a single-barrel ileo-cecal fistula.

The patient was re-admitted into the hospital two months later when an attempted but unsuccessful closure was made. He was discharged then to allow a wound infection to clear up. A spur clamp had been re-applied to obliterate the remaining inch of spur between the ileum and colon and about nine months after the first stage the patient was re-admitted to the hospital. After a few days of pre-operative care, the continuity of the bowel was re-established as a final stage Mikulicz procedure. Practically primary union resulted (Fig. 4).

PATHOLOGICAL REPORT*

Macroscopic Description: The specimen as delivered to the laboratory consists of a piece of resected cecum with the appendix and ascending colon measuring when opened 15 cm. in length and 11 cm. in width. Two cm. from the blind end of the cecum at the level of the ileocecal valve, the wall is occupied by an annular tumor measuring 8 cm. in length and 4 cm. in width. The surface is eroded, the base friable. The edges are heaped up and hemorrhagic. A dense mass of inflammatory tissue is adherent to the serosa. Grossly no involved lymphnodes are recognized (Fig. 5).

Microscopic Description: Sections through the gross tumor are composed of huge irregular tubular glands lined by one or more layers of columnar epithelial cells with large irregularly placed hyperchromatic nuclei frequently containing considerable amounts of mucus. These glands extend deeply into the muscularis and in the subserosa where the mucoid character becomes predominant so that in places the glands are replaced by huge cystically dilated mucoid containing spaces in which bits of the lining epithelium are present. Surrounding the glands both on the surface and in the depths is a rather pronounced fibrosis and lymphocytic infiltration. There is no apparent penetration of glands into the vascular or lymphatic spaces.

Sections of the gut proximal to the tumor show a marked

fibrosis of the mucosal stroma, in places forming shallow papillae covered by a somewhat hypertrophied but regular and unicellular epithelial layer. Immediately contiguous to the neoplasm there is a pronounced hyperplasia and hypertrophy of the mucosal glands and a marked increase in mucus both within the cells and within the gland lumens so that here and there mucus containing cyst-like spaces are present; these are lined by regular epithelium. This picture is also present in the appendix where a considerable lymphocytic and some polynuclear leucocytic infiltration is present in all the layers more particularly in the fibrosed mucosal stroma. In the sections taken from the appendix, the ileum and tumor itself there is a pronounced hyperplasia of the subendothelial connective tissue of the arteries, and to a lesser extent the veins. Frequently complete obliteration is noted as a result of this hyperplastic tissue or by fibroblasts which invade the bland thrombus in the vessels which generally show some degree of re-vascularization.

Sections of the cecum and colon distal to the neoplasm show only a moderate lymphocytic infiltration of the submucosa and muscularis. All the sections show the serosa covered by a fibrinous exudate.

Diagnosis: Primary gelatinous adeno-carcinoma of the cecum, with (obstructive) hypertrophy and hyperplasia of ileal and appendiceal walls.

SUMMARY

1. The literature on intussusception in the adult is reviewed.

2. It is shown that intussusception does not occur frequently in the adult and when it does occur it is usually chronic.

3. Intussusception usually follows Hunter's Law, "The upper segment invaginates into the lower segment," nevertheless a number of retrograde intussusceptions have been reported.

4. The probable causes and mechanics of intussusception are discussed.

5. A case of chronic intussusception in a male 35 years of age is fully reported including the clinical investigation, the surgical procedure and the pathological report.

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*From the pathological laboratories of the Beth-El Hospital, Dr. Mendel Jacobl, Director.

Abstracts

ABRAHAM, MARGERY AND WIDDOWSON, ELSIE.

Modern Dietary Treatment. (William Wood and Company, Baltimore, Md., 1937).

This book of 328 pages is like a grain of wheat from which the chaff has been removed. It is short and readable.

The opening two chapters are devoted to the principles of nutrition, dealing with carbohydrates, fats, proteins, minerals, vitamins, roughage, alcohol and water, and giving a table of the main sources of the various food essentials.

The next eight chapters are devoted

to a discussion of high and low calorie diets; invalid diets, including fevers, convalescence, fractures and heart disease; diseases of the alimentary system, including peptic ulcer, gall bladder, liver, pancreatic and colon disease; diabetes; kidney disease; metabolism; B. coli infections; epilepsy and rheumatism; and diets for Jewish patients. These various subjects are by no means given adequate or comprehensive treatment, presumably because the authors are not physicians. Although these chapters might be criticized for such primer-book presentation, they may suffice for the purposes for which this book was designed.

The last four chapters, in volume representing more than half of the book, are composed of food tables, diets and recipes, and rather comprehensive tables of the chemical composition of foods.

The extensive bibliography attests the amount of work expended in the concise compilation of this book. The index is well prepared.

Written and published in England some of the diets would be impractical in certain portions of the United States, but enough material can be found in the tables to make this a useful hand book of dietary treatment.

B. B. Vincent Lyon
and B. G. Gledhill.

BRUGER, M. AND FITZ, FRED.

Experimental Atherosclerosis: I. Effect of Prolonged Administration of the Thyrotropic Factor of the Anterior Lobe of the Pituitary on Experimental Atherosclerosis in Rabbits.

The authors refer to the original observation of Murata and Katoaka (1917) that the feeding of iodine prevented the deposition of cholesterol in the arterial walls, and that thyroidectomy (Turner and Khayat, 1933) abolished this protective action.

The present study was undertaken to determine what effect the pituitary gland, through its elaboration of the thyrotropic factor, exerts on experimental atherosclerosis in rabbits. Six groups of young rabbits were studied as follows: first, controls; second, rabbits to which 0.5 cc. thyrotropic factor only was administered 6 days per week; third, to which 1 gm. cholesterol 3 times per week and 1 cc. normal salt solution 6 times per week were administered; fourth, to which 1 gm. cholesterol 3 times per week and 0.25 cc. thyrotropic factor 6 times per week were administered; fifth, to which 1 gm. cholesterol 3 times per week and 1 cc. thyrotropic factor twice a week were administered,

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tain 650 or more international units of vitamin A; even prunes with only 350 units in two ounces contain over one-tenth of the infant's total daily requirement. (3)

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VEGETABLE SOUP

1. The Avitaminoses, Eddy and Dall-dorf. The William & Wilkins Co. (1937)
2. Council on Foods, Jour. Amer. Med. Assoc., 104, 1239. (1937)
3. Hanning, Jour. Amer. Diet. Assoc., 12, 231. (1936)
4. Eddy, Kohman and Halliday, Inc. & Eng. Chem., 21, 347. (1929) Iowa Agric. Exp. Sta. Report for 1933, 114.

and sixth, to which 1 gm. cholesterol 3 times per week and 1 cc. thyrotropic factor 6 times per week were administered. The animals were treated thus for about 120 days each before being killed for study. The entire aorta was then removed and the total cholesterol and ester cholesterol determined by standard methods. Throughout the period of observation the whole blood cholesterol was determined every 15 to 17 days in each rabbit.

The results showed that the continued administration of the thyrotropic factor alone over a protracted period of time exerts little influence on the cholesterol content of the aorta. When cholesterol and normal salt solution are administered there is an increased cholesterol content found in the vessel wall without much change in the ratio of ester to free cholesterol content. When, however, cholesterol and thyrotropic factor are given together to rabbits over a prolonged period, there appears in many instances a greater deposition of cholesterol in the aorta and the ratio of ester to free cholesterol is frequently elevated.

In the main the authors found that the cholesterol content of the aorta appeared to vary directly with the average concentration of cholesterol in the blood. There were 21 rabbits used in the entire study and this conclusion is based upon this number of observations. Those rabbits which received the thyrotropic factor in addition to cholesterol showed, as a rule, a greater deposition of cholesterol in the aorta than in those rabbits given cholesterol alone, but the average cholesterol content of the blood in each group remained about the same. This observation that in experimental rabbits the extent of arteriosclerosis, as gauged by the cholesterol content of the aorta, varies directly with the degree of hypercholesteremia, is at variance with the findings of Lundé and Sperry who studied the lipid content of the aorta and the concentration of cholesterol in the blood serum of 123 healthy persons who met with violent death and in whom there was found no relation between the degree of atherosclerosis in the aorta and the concentration of the cholesterol present in the blood. (As the above variance in observations may be of fundamental importance in the final understanding of atherosclerosis in man, it would seem important that further and more extensive studies along the same lines be made. The influence of the thyrotropic factor used in the above experiments may have been primarily in the nature of an injury to the vessel wall which permitted a secondary deposition of the cholesterol—Reviewer).

N. W. Jones, Portland.

PHELPS, KENNETH A.

The Early Treatment of Chemical Burns of the Esophagus. Jour. Lancet, 58:237-238, May, 1938.

Chemical erosion of the esophagus belongs in the class of serious and painful diseases. When a corrosive fluid is swallowed, necrosis of the mucous membrane occurs and the depth of the necrosis depends upon the concentration of the poison, and also upon the length of time it is in contact with the mucosa. As the necrotic tissue sloughs off, an ulcer forms and spasm occurs in an attempt to immobilize the ulcer and diminish pain. This stage of acute stenosis is reached in from 3 to 5 days,

while the resistance of the walls of the esophagus has not suffered. This is the time to start treatment without fear of perforation. If treatment is neglected, the opposing granulations grow, and produce a fold-like stenosis, which will increase the danger of perforation. The final stage is the replacement of the inflammatory infiltration by bands of scar tissue, resulting in stricture. Early treatment prevents this.

Salzer recommends the use of an elastic esophageal bougie, filled with lead shot, beginning on the second day, leaving the bougie in place a minute or two. The time is gradually increased on subsequent days to 30 minutes a day by the sixth day. The author has found

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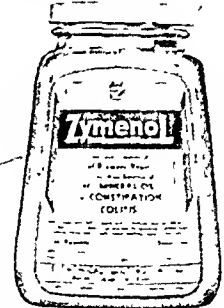
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any bougie or even a soft stomach or feeding tube to work as well. Starting treatment early is the important factor.

A case is reported of an old stricture complicated by fatal brain abscess following attempts at dilatation over a period of three years.

Hanes M. Fowler, Fort Wayne.

LOCKHART-MUMMERY, J. P.

The Causes of Hemorrhage from the Rectum. British Med. Jour., 1937-1938, May 7, 1938.

Bleeding from the rectum is a condition which is always of considerable concern to the patient and one which should be thoroughly investigated in

order to determine its cause and significance. Probably two-thirds of all cases of rectal bleeding are due to internal piles, and such a condition can generally be recognized by a simple examination of the rectum with a speculum. It is well to remember that the presence of internal piles does not exclude the possibility of a carcinoma higher up the bowel.

The next commonest cause of rectal bleeding is carcinoma. The diagnosis is, as a rule, readily established if a finger is passed well up into the rectum as probably 80 per cent of rectal growths occur within reach of the finger. Digital and sigmoidoscopic examination should be done before an X-ray is ordered. An

innocent adenoma will cause hemorrhage and it should be removed, as there is grave danger of it becoming malignant.

Hemorrhage due to peptic ulcer generally results in tarry stools due to partial digestion of the blood, but where the bleeding is copious or rapid and the bowels are not loaded the blood may be seen in the stools as bright fresh blood. A rare and obscure cause of rectal hemorrhage is a peptic ulcer in Meckel's diverticulum which is apt to occur in young persons. Another rare cause of rectal bleeding is an angioma of the rectum or sigmoid. Local injury must be remembered as a possible cause of bleeding from the rectum. Hemorrhagic or ulcerative colitis may cause rather serious bleeding but rarely serious enough to endanger life. Bleeding from the rectum may occur in persons with very high blood pressure, and may be profuse, and the pressure considerable reduced thereby.

Hemorrhage is a complication that occurs after operation upon the rectum in about one per cent of cases. The most common time for hemorrhage is about the eighth day after operation. The use of a small tube inserted in the rectum will usually stop small hemorrhage and will eliminate the possibility of concealed bleeding. In cases of persistent bleeding the rectum should be packed by means of a rubber tube with gauze wrapped around on end in figure of eight fashion to form a bulge, which is inserted through a speculum. The pack is anchored firmly in place by means of a safety pin and gauze around the part of the tube projecting from the rectum.

Hanes M. Fowler, Fort Wayne.

VON GLAHN, WILLIAM C., FLINN, FREDERICK R. AND KEIM, W. FRANKLIN, JR.

Effect of Certain Arsenates on the Liver. Arch. Path., 25:4-488, April, 1938.

The authors report a series of experiments on rabbits in which cirrhosis of the liver was produced by the continued administration of small amounts of arsenic in the food.

The experiments were undertaken because during a study of the effect of various diets on the liver of the rabbit in a series of ten rabbits fed on cabbage only pigment was found increased in the liver cells of most of the animals and in many of them large phagocytes containing pigment were present in the sinusoids. On repeating these experiments three times similar changes were not produced and the thought came to them that possibly the cabbage fed to the first series of rabbits might have been treated with one of the insecticides frequently employed for the spraying of fruit trees and vegetables. Lead arsenate, one of the commercial



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BILE SALT THERAPY IN GALL BLADDER DISEASE	Henry Doubilet, M.D., Harry Yarnes, M.D. and Asher Winkelstein, M.D.
THE SYMPTOMATOLOGY OF GASTRITIS	James B. Carey, M.D.
ESOPHAGEAL VARICES IN PORTAL HYPERTENSION. (PATHOGENESIS AND DIAGNOSIS BY ROENTGENOGRAPHY)	Milton Plotz, M.D. and Nathaniel E. Reich, M.D.
THE GASTRO PUMP	Samson A. Seley, M.D.
CLINICAL COURSE OF CHRONIC ULCERATIVE COLITIS	M. H. Streicher, M.D.
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THE GASTRIC SECRETORY CURVE BEFORE AND AFTER THE MANN-WILLIAMSON OPERATION, AND ITS BEARING ON THE NORMAL REGULATION OF GASTRIC ACIDITY	Charles M. Wilhelmj, M.D. and Rex W. Finegan, M.D.
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products commonly used for this purpose, was bought in the open market and used in some of the animals. This product is 98 per cent lead arsenate. Cupric arsenate, another commercial product was also used; and, in order to control any changes that might result from the lead and the copper of these products, chemically pure sodium arsenate was fed in another series.

Besides rabbits, experiments were also conducted on rats and ferrets. A biopsy on the liver was performed on each animal some days before the experiment was started. Then as samples of cabbage to be fed were found to contain 4.32 mg. of arsenic per kilogram comparable amounts were added to all of the diets. Oral administration was employed, as this is the manner in which arsenates contaminating food products gain entrance to the body.

Three diets varying in the carbohydrate content were used: namely, hay and oats with forty-six rabbits; hay, oats, carrots and cabbage with eighteen rabbits; and white bread and potato was fed to twenty-six. Each series was divided into three groups, the animals of which were given copper arsenate, lead arsenate and sodium arsenate respectively.

The lesions in the liver resulting from the ingestion of the different arsenates were similar in all. As early as the third day necroses of liver cells were found. These necroses were sharply defined from the surrounding liver cells. The necrotic cells were swollen and pale staining, at times the cytoplasm was transparent and the nuclei fragmented or destroyed. They were most frequently situated near the portal areas, sometimes surrounded it completely; sometimes they extended from one portal area to another. At times small groups of intact liver cells were surrounded by necrotic areas. About the necrotic areas were many large phagocytic cells, many with multi-nuclei. Later the necrotic liver cells were removed and there remained a mass of delicate fibrillar material which appeared to be collapsed stroma, and into these areas at a still later period fibroblasts penetrated and caused definite scarring. The gross appearance of the livers was altered in many of the animals. Usually the organ was smaller than normal and the capsular surface irregular or pebbled. Jaundice was present in some. Glycogen was reduced in the liver cells. In brief the livers in rabbits living but 2 or 3 days showed as a rule necrosis of some of the cells. When the animals lived longer, that is, from a month to a year or more, most of the livers showed the presence of a true chronic cirrhosis. There were some exceptions.

The animals to which carrots and cabbage were added to the diet showed a lessened degree of necrosis of the liver cells and an earlier grade of cirrhotic change than found in the

livers of those rabbits fed on hay and oats only. In the twenty-six rabbits fed on white bread and potato, a minimal cirrhosis was found in only two animals. A few scattered hepatic necroses were found in but three. The phagocytic cells were less numerous and the deposition of pigment less marked. Considerable glycogen was found in the liver cells. It seemed evident that the presence of carbohydrate had protected the livers from damage. This observation corresponds to a similar observation in man by clinicians.

Fifty-one rats and fifteen ferrets were studied in a series in like manner. In no animals was there observed any necrosis of the liver cells or a single instance of cirrhosis. These experiments merely showed that so far as damage to the liver is concerned, these animals are more resistant to the effect of arsenates than are rabbits.

Under the controlled conditions of the experiments it may be concluded that the lesions in the liver are the direct result of the effect of the arsenates upon it; that the lead and copper

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from symptoms, a proctoscopic and digital examination showed marked narrowing of the rectal lumen due to rectal edema and hypertrophy of the wall. Autopsy, four months later, revealed an edema and true fibrosis of the wall. There was no evidence, gross or microscopic, of rectal malignancy.

Case II. A male, 72 years, also received two series of radiation for prostatic malignancy, with favorable effects, from May 22 to Dec. 4, 1935. In this case, rectal symptoms appeared soon, about two months after the start of

radiation. Fecal incontinence was present off and on until April 17, 1937, when symptoms of intestinal obstruction appeared. On rectal examination there was marked edema of the wall with narrowing of the lumen and a mass in the lumen, probably fecal. The patient failed to improve with local measures and a colostomy was performed. He died two hours after the operation. The observations at autopsy indicated that compression of the rectum by metastatic lesion was not sufficient in itself to produce complete

obstruction, but the edema and fibrosis of the rectal wall was quite a factor.

The intimate anatomical relationship of the rectum to the other pelvic organs accounts for its involvement when any of these organs is subjected to intensive radiation therapy.

Although in each of the above cases the malignant lesion had not been eradicated by the radiation and early death was inevitable, it is believed that the recognition of such rectal stenosis in certain other patients, in whom the primary lesion is under control, may lead to appropriate surgical therapy and be life saving.

It is important that the author has called attention to the occasional dangerous effects of over-radiation in numerous cases of intra-abdominal cancer. Although he has reported only two cases of stenosis of the rectum in his general discussion of the subject, he found in the literature that the frequent unhappy result occurs following radium treatment for carcinoma of the cervix. Of 18 cases treated by Everett, seven developed vesico-vaginal fistula and eleven bilateral ureteral stricture. The experiences of other authors also are quoted such as Bule and Malmgren, Newell and Crossen, Jones and Ferguson.

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PORTIS, SIDNEY A.

Should We Operate On All Our Cases of Gall Bladder Disease? Radiologic Review and Miss. Valley Med. Jour., 60:90-93, May, 1938.

Since the introduction of the Graham-Cole test and the increasing skill of the surgeon in removing presumable disease of the gall bladder, more and more surgery has been done in recent years for bile tract disease. The author raises the question as to whether or not all this surgery is warranted, especially in cases of mildly diseased gall bladders.

Attention is called to possible errors in technique causing a non-visualization of the gall bladder. One of the most common sources of error is that many patients have a meal containing fat shortly before the dye is given by mouth. Another reason for non-visualization is that the liver may retain the dye and fail to secrete it, owing to disturbed liver function.

Patients who have gall stones, a markedly diseased gall bladder, or a non-visualized gall bladder should be operated upon unless contra-indications exist. Many patients, particularly those who have had mildly diseased gall bladders removed, complain of symptoms similar to those they had previous to operation. It has been shown that many of these patients suffer from acute spasm of the sphincter of Oddi with enlargement and distention of the common duct. The spasm is relieved by

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Drastic chologogues should be omitted in the medical management of gall bladder patients. Hypomotility and stasis of the gall bladder is frequently seen in hypothyroid states and marked clinical improvement is often seen when adequate thyroid is given. It is believed that foci of infection may be a factor in gall bladder disease by setting up an allergic response in the gall bladder. Patients are frequently seen with gall bladder disease and an associated myocardial condition and an improvement of the myocardial condition has an associated improvement in the gall bladder picture.

Adequate pre-operative preparation is most important in attempting to lower the surgical mortality in patients with bile tract disease. The patient should be on a pre-operative diet for several days prior to operation and laboratory work should include the following—urinalysis, complete blood count, Wassermann and Kahn, bleeding and coagulation time, and blood chemistry to include non-protein nitrogen, blood sugar, icterus index, and albumin-globulin ratio. Suitable donors should be ready if transfusion becomes necessary. Patients whose albumin-

globulin ratio, icterus index, or cholesterol ester fraction of the total cholesterol are not within normal limits, are poor surgical risks.

Postoperatively gall bladder patients should have plenty of glucose, intravenous fluids, and carbon dioxide inhalations to expand local regions of atelectosis. The diet should be gradually increased to one similar to the pre-operative high-carbohydrate, low fat diet. There should be no urgency for surgery of the bile tract except in cases of suppurative cholecystitis or possible gangrene of the gall bladder.

Cases of gall bladder disease which are intractable to medical management, those that have gall stones, and those cases with associated pericholecystic disease should have surgical intervention. Those cases of functional disturbance, particularly the so-called cholesterosis of the gall bladder or "strawberry gall bladder" had better not be treated surgically, but medically, because these patients are as a rule most uncomfortable following surgical intervention.

Pre-operative and post-operative diets are outlined.

Hanes M. Fowler, Fort Wayne.

LOE, RALPH H.

Gastroscopic Examinations—A Review of 80 Cases. Northwest Med., 37:139-142, May, 1938.

Gastroscopy is a safe, relative painless procedure which gives a clear picture of the interior of the stomach. It is a valuable adjunct to use in clarifying questionable roentgen defects of the stomach. The accuracy of the findings depends upon the skill and ability of the examiner. The fault of misrepresentation rests upon the one making the examination and not on the instrument.

Gastroscopy is of value in determining whether an ulcer is benign or malignant. It may aid in determining the operability of a carcinoma of the stomach, and its usefulness may be enhanced in this respect by using it in conjunction with the peritoneoscope. Gastroscopy offers possibilities of definite diagnosis in the late sequelae of postoperative stomachs. It is supreme in the diagnosis of chronic inflammatory lesions such as the superficial, atrophic, and hypertrophic types of gastritis. This discussion is based on a review of eighty cases examined by the author.

Hanes M. Fowler, Fort Wayne.

QUICK, A. J.

The Nature of Bleeding in Jaundice. J. A. M. A., 110:1658, May 14, 1938.

The author presents experimental observations made on the coagulation of the blood which furnishes significant information on the nature of cholemic bleeding and offers practical suggestions for the management of jaundiced patients. He has developed a simple method for the determination of prothrombin. This is done by observing the clotting time of oxalated plasma when mixed with an excess of thromboplastin and an optimum amount of calcium. When the thromboplastin and calcium are constant the rate of coagulation depends on the concentration of prothrombin and is a direct means for determining this factor.

Prothrombin determinations were also made on both normal and abnormal individuals and it was found that in normal individuals it was constant. In hemophilic blood it was found to be quantitatively normal while in jaundiced patients it was found to be extremely low in some cases. This deficiency of prothrombin has been shown to bear a direct relationship to the severity of the bleeding. Therefore experimental reduction of prothrombin was brought about in three ways: first, by vitamin K deficiency, second, by a toxin (spoiled sweet clover hay), and third, by injury of the liver.

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thought that bleeding in jaundiced patients might be due to a deficiency of vitamin K or liver destruction. These cases must be treated first by transfusion in order to bring about an immediate increase in the prothrombin and then by the administration of vitamin K in the form of powdered alfalfa leaf or an extract of it.

Francis D. Murphy, Milwaukee.

MCGREGOR, JOHN AND ROTHENBERG, MORRIS.

Congenital Absence of Portion of Small Intestine. Northwest Med., 37:124-126, May, 1938.

The authors report a case of congenital absence of a portion of the small intestine. An attempt was made to correct the condition surgically by a side to side anastomosis. The surgery was accomplished without difficulty but the patient died 14 hours after the operation.

The two segments of the intestine ended in blind pouches near the lower border of the liver. The mesenteries of both were free and terminated at the end of each pouch, thereby forming two free borders.

The incidence of the condition is not at all common. Various authors report its incidence to be from 1:20000 to 1:3150 births. Surgery is the only treatment and it is essential that dehydration and alkalosis be combatted both pre and post-operatively. The mortality is about 100%.

References are given to articles with excellent discussions on the possible etiology and classification of intestinal anomalies.

Hanes M. Fowler, Fort Wayne.

CARMICHAEL, JOHN L.

Hyperinsulinism Associated with Hypothyroidism: Two Case Reports. Annals of Int. Med., 11: 1906-1911, April, 1938.

A review of the literature reveals an indication of a mutual antagonism between the thyroid and islet secretions. No attempt is made to determine whether the antagonism is direct or through the intermediary of some gland such as the pituitary.

Two cases of hyperinsulinism associated with hypothyroidism are reported. In both cases the glucose tolerance test more closely approached the normal response after the basal metabolic rate had been raised to the normal level by feeding desiccated thyroid.

The author concludes that some cases of hyperinsulinism may be improved, if not entirely held in check, by the use of desiccated thyroid, but it is realized that results of such treatment in a large number of cases followed over a long period of time would be necessary be-

fore any trustworthy conclusions could be drawn.

Hanes M. Fowler, Fort Wayne.

ISRAEL, SIDNEY.

Esophageal Obstruction: Case Reports. Texas State Jour. of Med., 33:828-830, April, 1938.

Esophageal obstruction manifests itself with either sudden or gradual onset. Those of sudden onset are generally due to swallowing of a foreign body or an injury, while those of gradual onset are usually due to local inflammation, benign or malignant neoplasms, syphilis, neuropathic functional disturbances, or extrinsic pressure as from mediastinal or glandular involvement.

The most important aids in diagnosis are a complete detailed history, X-ray examination using a thin barium mixture, and esophagoscopy examination under local or general anesthesia as the case demands.

Three cases are reported illustrating obstructions due to stenosis, foreign body, and ulcerated lesions.

Hanes M. Fowler, Fort Wayne.

HUNT, H. B.

Ascorbic Acid in Bronchial Asthma. British Med. Jour., 723: 727, April 2, 1938.

The author reviews the literature relative to the subject and reports the results of treatment in twenty-five cases. The investigation did not show ascorbic acid to be of any value in the treatment of bronchial asthma when given in comparatively large doses either by injection or by mouth.

Hanes M. Fowler, Fort Wayne.

EVANS, N. AND GRAY, P. A.

Laënnec's Cirrhosis. J. A. M. A., 110:1159, April 9, 1938.

Due to the fact that the etiology of Laënnec's cirrhosis is still being debated by clinicians and pathologists, the authors have reviewed 217 cases of it with special reference to its etiology. In examining records of 17,874 autopsies from January 1, 1918, to May 1, 1937, 217 cases were found, an incidence of 1.2 per cent. Arranged chronologically these cases show a definite rise in incidence since the repeal of prohibition. The incidence since repeal is three times that before. One-fourth of the patients were chronic alcoholics, most of whom were males.

In those cases in which cirrhosis was not present, but a history of chronic alcoholism was, the liver frequently showed fatty changes. The authors conclude that chronic alcoholism is definitely a contributing factor in the aforementioned disease.

Francis D. Murphy, Milwaukee.

BASIC OPERATIONS IN COMMERCIAL CANNING PROCEDURES

V. HEAT PROCESSING THE SEALED CONTAINER

● Previously, we have described how raw food material is sealed in the tin container after proper preparatory treatment. After sealing, the next important step in commercial canning is the heat process, or "process" as it is called in the industry.

Essentially, the processing operation involves exposure of the sealed container to hot or boiling water, or to steam under pressure, for the correct period of time. The purpose of the process is to destroy pathogenic or spoilage organisms which may be present on raw food material; the seal on the can then prevents re-infection of the foods by such organisms. Thus, the sealing and processing operations combine to insure a sound, wholesome canned product.

It is not possible here to review all factors which must be considered in the establishment of an adequate heat process for any specific product. Such factors have been briefly discussed in recent publications (1, 2). It must suffice to state that, in general, commercial processing operations are divided into two general types, depending upon the acidity of the food being canned.

The "acid" foods—including the common fruits and certain vegetables or vegetable products whose pH values fall below 4.5—are quite easily heat processed. With such foods it is only necessary to heat the sealed container long enough to permit the attainment of a definite temperature

in the center of the can (usually 200°F. or slightly less). In fact, some acid products may be processed by filling sufficiently hot, sealing and inverting the cans, and cooling without further process.

The "non-acid" foods—such as meat, sea foods, milk and most of the common vegetables—require temperatures above that of boiling water for adequate heat processing. Such foods are processed under steam pressure in a closed "retort", usually at a temperature of 240°F. Years of research have made possible the issuance for the guidance of modern canners of a bulletin listing recommended process schedules for the non-acid products (3).

Regardless of the temperature of processing, equipment is available which permits use of the batch or "still" process, and the "continuous" or "agitating" types of process for sealed cans. Improvements in processing machinery and accessory instruments during the past two decades permit precise, scientific control of commercial processing operations.

Above all, however, the modern canner has a clear understanding of the underlying purpose of the process and a deep appreciation of the necessity for strict supervision of the processing operation. Commercially canned foods, consequently, must be ranked today among the most wholesome foods coming to the American table.

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(1) 1938 Food Research 3, 13

(2) 1937 J Amer. Med. Assn 129, 1946

(3) 1937 Natl. Canners Assn. Bull. 274, 3rd ed.

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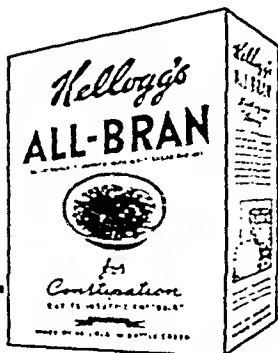
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WARING, J. I.

The Nutritional Factor in Heart Disease in Children. Southern Med. and Surg., 100:119-121, March, 1938.

The author calls attention to heart disease due to nutritional deficiencies as observed in Negro children in Charleston, S. C. The essential findings are those of an enlarged heart with impaired function with a tendency to generalized edema. The cases summarized are not consistent in pointing to a lack of vitamin B₁ as the usual basis of the disease, but suggest a rather more general deficiency of dietary materials. They indicate that a satisfactory response to dietetic treatment may be expected in cases not too far advanced.

Hanes M. Fowler, Fort Wayne.

ATKINSON, A. J. AND IVY, A. C.

Does Removal of a Normal Gall Bladder Affect the Metabolism of Lipids? Jour. of Laboratory and Clinical Med., 23:441, Feb., 1938.

As a result of experiments on dogs, the authors conclude that the rise in fasting plasma lipid levels obtained after cholecystectomy is not specifically due to removal of the gall bladder. It may also be obtained after liver damage, tissue injury, and for a short time after ether or chloroform anesthesia. By studying the blood lipids (total fatty acids, free and total cholesterol) before and after cholecystectomy both under the condition of fasting and during the digestion and absorption of fat, it could not be demonstrated that the gall bladder possessed a function of regulating the metabolism of lipids.

Hanes M. Fowler, Fort Wayne.



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ALICATO, J. E. AND SCHLATTENBURG, O. L.

A Case of Intestinal Heterophyidiasis of Man in Hawaii. J. A. M. A., 110:1100, April 2, 1938.

Heterophyid infestation of the intestine in man has been reported from such far eastern countries as China, Japan and Korea, but never before in Hawaii. The case was that of a 26 year old Japanese man who, six weeks before examination had developed a diarrhea which was severe and lasted about three weeks. He had lost about 20 pounds in weight and had a corresponding loss of body strength. When first seen he complained of nervousness and constant discomfort over the colon which was not influenced by the intake of food, defecation or mechanical pressure. His history was essentially negative except for the fact that he liked to eat raw fish, especially "fresh water" mullet and "Chinese eat fish."

Physical examination was essentially negative. Laboratory examination revealed the urine to be negative, the stool negative for amoeba and occult blood. The Weil-Felix test, the Widal test, and the Wassermann and Kline tests were negative. The blood count on one occasion was: hemoglobin 75 per cent, red cells 4,956,000, white cells 9,100, polymorphonuclear leukocytes 47 per cent, basophils 7 per cent, eosinophils 2 per cent, small lymphocytes 44 per cent. On another occasion the white count showed a total of 7,100 of which 37 per cent were polymorphonuclear leukocytes, 4 per cent eosinophils, 12 per cent monocytes and 47 per cent small lymphocytes. Roentgenologically the gastro-intestinal tract was negative except for some irritability of the colon.

Stool examinations were continued and fluke ova were found of the genus *Stellantchasmus*, closely related to, if not identical with, *Stellantchasmus falcatus*. The patient

was placed on oleoresin of aspidium which cleared the condition up rather promptly.

Investigation of local mullet fish in surrounding waters revealed infestation with a heterophyid fluke which was pathogenic for cats. Francis D. Murphy, Milwaukee.

DRUECK, CHARLES J.

Proctitis. Illinois Med. Jour., 73:438-441, May, 1938.

Proctitis, rectitis or inflammation of the rectal mucosa is probably the most frequently encountered of all rectal affections. It is of more common occurrence than generally supposed and is also directly responsible for the production of many disturbances which in turn give rise to symptoms mistaken for distinct diseases. The discussion is confined chiefly to catarrhal proctitis and sigmoiditis, acute and chronic, among the causes of which may be listed the following: irritants such as worms, highly seasoned foods or hard substances in the fecal mass, fish bones and hulls of cereals, constipation and fecal impaction, irritating discharges from above, seasonal changes in food or water, use of strong purgatives, poisonous drugs, irritating suppositories and local extension of inflammation from hemorrhoids or disease of neighboring organs such as the bladder, prostate, vagina or uterus.

The symptoms include sensation of fullness, weight, heat and burning in the rectum, or in severe cases, actual pain that radiates to the sacrum or other pelvic organs or down the thighs. Rectal tenesmus is constant early. The process is essentially an acute inflammation of mucous membrane and resembles that seen in other parts of the body, e. g., the nose. The prognosis is usually good with proper treatment.

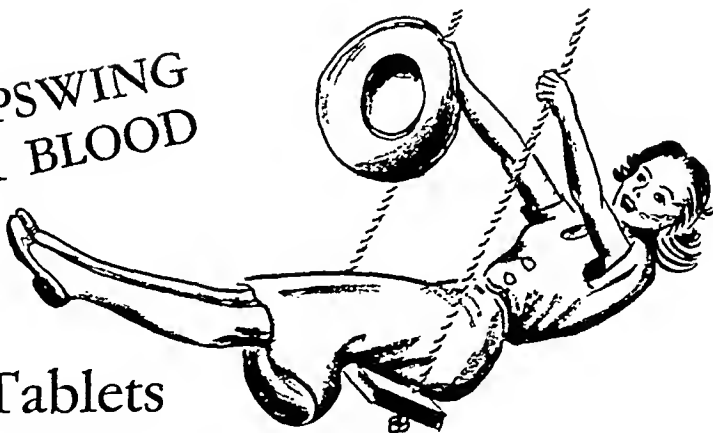
A system of treatment is outlined including careful inspection of the rectum, use of castor oil or saline cathartic

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followed by repeated irrigations of the colon with salt or boric acid solution at 110° F. Following the douching two drams of 25% solution of fluid extract of hydrastis is injected into the rectum to be retained. If ulcers are found on the rectal wall they are treated locally by painting with pure ichthylol or 5% silver nitrate solution.

The diet should be carefully arranged so as to be non-irritating and of such variety as will insure soft or semi-solid evacuations. As the inflammation subsides, constipation is apt to occur and a full glass of flaxseed tea at night will be found to act as a mild laxative and at the same time is soothing to the intestine. A recipe for flaxseed tea is given.

The patient should be kept in bed until all pus and blood have disappeared from the stools.

Hanes M. Fowler, Fort Wayne.

JOHNS, HENRY J.

The Outlook for Diabetic Children. Southern Med. and Surg., 100:103-110, March, 1938.

The author estimates that there are some 1000 new diabetic children each year who now live as compared to approximately 1000 diabetic children who died yearly in the pre-insulin era. Heredity is an important factor in the etiology of diabetes in that it is believed that the condition of the island apparatus is determined thereby. Infection is also an important factor, especially in precipitating active cases among so-called border-line cases.

As diabetic children reach adulthood and marry, attention must be directed to the hereditary aspects of the condition. A diabetic child is not necessarily handicapped physically or mentally provided his nutrition is kept up satisfactorily, which entails the proper use of diet and insulin.

One of the disquieting things in the management of diabetic children is the progressiveness of arteriosclerosis which seems to be appearing at an early age.

With the 15 years of the insulin era a complete transformation has taken place in the outlook for the diabetic child. With the facilities at hand for properly controlling the condition, diabetic children can now look forward to doing practically all the things that non-diabetics can do.

Hanes M. Fowler, Fort Wayne.

EDCOCKE, BANNER R.

Colonic and Rectal Cancer. Northwest Medicine, 57:81-83, March, 1938.

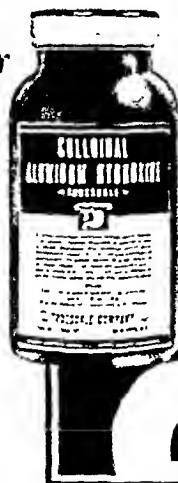
The author cites figures to substantiate his conclusion that the incidence of colonic and rectal cancer has increased during the past 15 years or so. He also stresses the importance of early recognition of the condition.

The incidence of rectal and colonic cancers is about equal, with about half as many located in the right side as in the left side of the colon. Gastric disorder, early tumefaction, and early cachexia are prominent symptoms of right-sided malignancy. Obstruction, partial or complete, and borborygmus are found more often in left-sided cancer, but seldom in rectal cancer. Bright blood in the stool must always be regarded as possible cancer. Sigmoidoscopy and colon roentgenogram should be demanded at once. These procedures should be repeated, if the bleeding persists, until its site has been determined.

The public must be informed of these early symptoms even at the risk of increasing cancerphobia and neurosis. The profession must be more alert in the early identification of colonic and rectal cancer.

Hanes M. Fowler, Fort Wayne.

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Studies in Absorption of Undigested Protein in Human Beings: VII. Absorption of Protein Introduced by Tube into the Duodenum*

By

IRVING GRAY, M.D.

and

MATTHEW WALZER, M.D.

BROOKLYN, NEW YORK

IN a previous study (1) the writers found that the rapidity of absorption of unaltered protein following its oral administration was directly influenced by the degree of gastric acidity. In the presence of hyperacidity, the absorption of unaltered protein was definitely retarded. In hypoacidity it was accelerated. In order to obtain further information on the factors influencing absorption from the upper digestive tract, it was decided to administer the test meal by duodenal intubation directly into the intestines. In this manner, interference with the emptying of the stomach could be excluded as a mechanical factor influencing the rapidity of absorption, and the importance of the acid role could be more clearly evaluated.

Peanut was the protein selected for this investigation. This choice was determined solely by the circumstance that there was available at the time a serum which was particularly suitable for the study of this antigen. This serum was the same one which had been employed in the previous study on absorption of proteins following its oral administration (1).

The method for determining the absorption rate is an immunologic one which has been described in great detail in previous communications (3). It may be briefly summarized as follows:

Peanut is excluded from the subject's diet for twenty-four hours preceding the test. One-twentieth of a cubic centimeter of a 1 to 10 dilution of the sensitizing serum is introduced intracutaneously on the forearm of the subject. (This serum had been obtained from a patient who manifested a very marked reaction to an intracutaneous test with peanut extract in a very high dilution and who was extremely sensitive clinically to this food). On the morning after the passive local cutaneous sensitization, the subject is given the peanut test meal on an empty stomach. The meal consists of a "milk" made by dissolving 10 grams of raw ground peanuts in 30 cc. of water, to which is added 1 gram of sugar and .05 cc. of oil of cloves. The entrance of the unaltered peanut protein into the circulation is marked by the onset of a reaction at the sensitized cutaneous site. Pruritis is usually the first symptom noted. Erythema and wheal formation follow rapidly. The absorption time is the interval which elapses between the consumption of the test meal and the appearance of the first objective sign at the sensitized site; namely, erythema or wheal.

For the administration of the test meal in the present study the duodenal tube was passed on a fast-

ing stomach and the position of the bucket was localized with the aid of the fluoroscope. When it was visualized in the duodenum and bile was obtained on aspiration, the peanut meal was injected through the tube.

Individuals with frank atopic illnesses, such as hay fever and asthma were not used as subjects for study.

TABLE I
Absorption times in cases with normal gastric acidity

Case No.	Age	Sex	Diagnosis	Absorption Time in Minutes
52	35	F	Chronic Cholecystitis	13
56	34	F	Chronic Cholecystitis	14
62	42	M	Gout	12
63	46	F	Chronic Cholecystitis	12
64	30	F	Pelvic Disease	20
65	55	M	Coronary Sclerosis	16
71	34	F	Chronic Cholelithiasis	16
76	36	M	Ulcerative Colitis, Chronic Proctosigmoiditis	20
78	56	F	Arteriosclerosis	19
79	28	F	Chronic Cholecystitis	19
80	18	F	Migraine	23
85	26	F	Gastric Neurosis	13
Average Absorption Time in Minutes				16.4

for it has been demonstrated (2) that such persons do not accept local cutaneous sensitization with the same degree and regularity as do normals.

The 46 subjects studied were adult patients of both sexes who, in most instances, suffered from some functional or organic disease of the gastro-intestinal tract. The diagnoses in these cases were arrived at after the completion of thorough laboratory, X-ray and clinical investigations.

The degree of gastric acidity was determined either by fractional gastric analysis or by a Boas test meal. In most instances, where an abnormal gastric acidity curve was obtained, the analyses were repeated in order to check the findings.

As in the previous study, the cases were roughly classified according to the amount of gastric acidity which they presented (1). Individuals who had a variation in free hydrochloric acid between 20 and 30 degrees and a total acidity between 30 and 40 degrees

*From the Department of Applied Immunology of the Jewish Hospital of Brooklyn, N. Y.
Read at the Spring Meeting of the Society for the Study of Asthma and Allied Conditions, Atlantic City, New Jersey, May 2, 1937.
Submitted November 10, 1937.

were considered normal. When the free hydrochloric acid was constant at 40 degrees or over and the total acidity constant over 60 degrees, a state of hyperacidity was considered present. In the hypoacidity group were placed those subjects in whom free hydrochloric acid was constant at less than 10 degrees and in whom total acidity was constant under 20 degrees.

TABLE II

Absorption times in cases with gastric hyperacidity

Case No.	Age	Sex	Diagnosis	Absorption Time in Minutes
54	46	M	Duodenal Ulcer	31
55	27	M	Duodenal Ulcer	29
59	29	M	Duodenal Ulcer	28
60	53	M	Duodenal Ulcer	20
67	31	F	Duodenal Ulcer	14
72	47	M	Pyloric Ulcer	23
73	43	M	Cholecystectomy	30
74	39	M	Duodenal Ulcer	25
77	29	M	Duodenal Ulcer	19
83	31	M	Duodenal Ulcer	20
Average Absorption Time in Minutes				23.9

Patients in whom no free hydrochloric acid was found were not encountered in the present study.

According to the above standards, 12 patients fell into the normal acidity group. The findings on these cases are summarized in Table I. The absorption times in this group varied from 12 to 23 minutes. The average for the entire group was 16.4 minutes.

In Table II are listed the results obtained in the 10 cases with hyperacidity. The absorption times in this group varied from 14 to 31 minutes. The average rate of absorption was 23.9 minutes.

In Table III are listed the ten cases with gastric hypoacidity. Among these the absorption time varied from 11 to 24 minutes. The average was 16 minutes.

Comparing the results obtained in these groups, it will be noted that, although there is little difference between the average absorption times of the normal and hypoacidity cases (16.4 and 16 minutes respectively) there is a definite delay in absorption in the hyperacidity group, the rate in the latter group being 23.9 minutes, an increase of 45.7% over the normal. This is virtually the same result which was obtained in the previous study when the peanut protein was given orally. Under those conditions, the normal average was 18.7 minutes and the hyperacidity average 27.5 minutes, an increase of 47% over the normal.

In the present study as in the previous one, the reading of the hypoacidity group differed less from the normal than did that of the hyperacidity group. When the meal was given directly into the duodenum the average reaction time in the cases with hypoacidity was 16 minutes, an acceleration of only 2.4% over the reading in the normal acidity group (16.4 minutes). In the oral study, the hypoacidity average was 15.9 minutes, an acceleration of 15% over the normal time (18.7 minutes). These results do not indicate an un-

equal influence on absorption by different degrees of acidity. The explanation for this variation in results probably lies in the arbitrary standards which were adopted for the classification of cases. The limits of acidity readings for the hypoacidity groups (all below 10° free and 20° total acid) are much narrower than those of the hyperacidity group (all above 40° free and 60° total acid).

The average absorption time for the entire series of 32 cases studied by duodenal feeding of the protein was 18.7 minutes. This was several minutes shorter than the average obtained in the previous study in which the peanut meal was given orally. A direct comparison of the results in the two series was not permissible, however, as the two studies were not made on the same subjects with the same batch of sensitizing peanut serum.

In order to obtain more reliable data on the comparative rates of absorption following oral and duodenal feedings of the antigen, a series of 14 subjects were tested by both methods, using the same serum. Only a few days were allowed to elapse between the oral and duodenal testings of each patient.

The results obtained in each subject by the oral and by the duodenal feeding of the antigen are listed in Table IV. In this group of 14 cases, the average absorption time following the duodenal administration of the protein was 18.6 minutes. This was more rapid by 5.7 minutes than the average oral time (24.3 minutes) in the same cases. In every subject but one, the duodenal administration of the antigen reduced the oral absorption time by a period varying from 1 to 17 minutes.

The influence of gastric acidity upon the rate of absorption of unaltered protein was again demonstrated in this comparative study (see Table V). With the

TABLE III

Absorption time in cases with gastric hypoacidity

Case No.	Age	Sex	Diagnosis	Absorption Time in Minutes
51	65	M	Carcinoma of Bile Ducts (Jaundice)	15
53	31	F	Chronic Cholelithiasis	12
57	23	F	Viscerosplenic	18
58	21	M	Colitis (Mucous)	17
61	38	M	Jaundice (Catarrhal Acute) Hepatitis	11
66	61	F	Pelvic Disease	24
75	27	F	Colitis	22
81	62	M	Carcinoma of Colon (Sigmoid)	15
82	28	F	Chronic Cholecystitis	13
84	56	M	Chronic Gastritis	13
Average Absorption Time in Minutes				16

duodenal as well as with the oral administration of the test meal, absorption was retarded in cases with hyperacidity and accelerated in individuals with hypoacidity, as compared to the normal acidity rate for each method of feeding.

It is also of interest to note that the differences between the oral and duodenal absorption rates mounted

as the degree of gastric acidity increased (see Table V). Thus, the absorption rate was less with duodenal than with oral feeding by 1.8 minutes in the hypoacidity group, by 6.2 minutes in the normal acidity cases, and by 9.3 minutes in the hyperacidity group.

Absorption studies upon unusual cases offered an opportunity to determine the influence of mechanical

delayed in both instances. They were 23 and 26 minutes respectively, whereas the average absorption rate for the normal acidity group of the same series (see study VI) (1) was 18.7 minutes and in the hyperacidity group 27.5 minutes. These findings clearly demonstrated that the delay in absorption in patients with gastric hyperacidity could not be attributed to

TABLE IV

Comparative study of absorption times after the oral and duodenal administrations of peanut protein in fourteen cases

Case No.	Age	Sex	Diagnosis	Gastric Acidity	Absorption Time in Minutes	
					Duodenal	Oral
71	34	F	Chronic Cholelithiasis	Normal	16	18
72	47	M	Pyloric Ulcer	Hyperacidity	23	33
74	39	M	Duodenal Ulcer	Hyperacidity	25	33
75	27	F	Colitis	Hypoacidity	22	27
76	36	M	Ulcerative Colitis, Chronic Proctosigmoiditis	Normal	20	37
77	29	M	Duodenal Ulcer	Hyperacidity	19	26
78	56	F	Arteriosclerosis	Normal	19	21
79	28	F	Chronic Cholecystitis	Normal	19	33
80	18	F	Migraine	Normal	23	24
81	62	M	Carcinoma Colon (Sigmoid)	Hypoacidity	15	18
82	28	F	Chronic Cholecystitis	Hypoacidity	13	9
83	31	M	Duodenal Ulcer	Hyperacidity	20	32
84	66	M	Chronic Gastritis	Hypoacidity	13	16
85	26	F	Gastric Neurosis	Normal	13	14
Average Absorption Time in Minutes					18.6	24.3

factors upon the rapidity of absorption of unaltered protein from the upper digestive tract.

Two patients, upon whom posterior gastro-enterostomies had been performed several years previously for the relief of chronic duodenal ulcers, were submitted to the absorption tests. Repeated gastric extractions on these individuals always revealed the presence of hyperacidity. Fluoroscopic and X-ray examinations disclosed in each case a normally functioning gastro-enterostomy. Despite the fact that the emptying time of the stomach in these patients was more rapid than normal, the absorption rates when the peanut test meals were given orally were found to be

TABLE V

Relation of the degree of gastric acidity to absorption times following oral and duodenal administration of peanut protein in fourteen cases

Degree of Gastric Acidity	Number of Cases	Average Absorption Time in Minutes	
		Oral	Duodenal
Hypoacidity	4	17.5	15.7
Normal	6	24.5	18.3
Hyperacidity	4	31	21.7

any tardiness on the part of the stomach in emptying itself.

Under certain circumstances, however, organic disease, which mechanically interferes with the normal function of the pylorus may be responsible for delaying the absorption of ingested protein. This was well illustrated in three patients with gastric carcinomas which, in each instance, produced incomplete pyloric obstruction. Gastric extractions revealed little or no free hydrochloric acid in these cases. Following the oral administration of the peanut meals, the absorption rates were 46, 51 and 62 minutes respectively. These were far in excess of the averages for the other hypoacidity and anacidity cases in the same series, which were 15.9 and 11.7 minutes respectively (see Study VI) (1). These findings demonstrate that the mechanical interference with the passage of food from the stomach into the duodenum can and does delay the absorption of unaltered antigen into the circulation. They also offer suggestive evidence that there is no absorption of undigested protein from the stomach itself in pathologic cases of this type.

SUMMARY

1. Following the intra-duodenal administration of a peanut test meal, the rate of absorption of unaltered peanut protein is more rapid by several minutes than the rate following its oral consumption.

2. In patients with gastric hyperacidity the absorption rate from the duodenum is not as rapid as in those with normal gastric acidity.

3. In patients with gastric hypoacidity the absorption rate from the duodenum is more rapid than in patients with normal gastric acidity.

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Bile Salt Therapy in Gall Bladder Disease*

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THE symptoms of chronic gall bladder disease may be divided into three distinct groups: (1) pain, commonly called biliary colic, (2) indigestion, or dyspepsia, under which may be included pyrosis, belching, gaseous distention and flatulence after meals, and (3) constipation. The attacks of pain are not colicky in nature in the true sense of the word, since the pain may last continuously without intermittent periods of freedom, anywhere from ten minutes to several days. The pain commonly starts in the epigastrium or right upper quadrant and tends to spread to right and left in a girdle fashion, and upwards to the right shoulder blade. It is usually described as either compressing or distending in character. Very often there is present in addition a penetrating pain, which passes through directly from the epigastrium to the back. Depending on the individual, the pain may be felt in all these regions, or in one place only.

Following cholecystectomy it is estimated that the attacks of pain recur in approximately 20% of cases (1, 2), usually somewhat milder in character but occasionally as severely. This recurrence is blamed on residual or newly formed common duct stone or intra-hepatic stones, recurrent pancreatitis, duodenal adhesions, hepatitis, or spasm of the sphincter of Oddi. A stone in the common bile duct is occasionally found at a subsequent operation. Rarely there is definite evidence of pancreatitis. Very often no explanation can be offered except the possibility of recurrent spasm of the sphincter of Oddi. This is known to exist in the human and this idea is supported by observations that attacks tend to occur during states which may be accompanied by gastro-intestinal spasm, i.e., periods of emotional upset, during the menopause in women, and following periods of severe constipation. In addition it has been noted that occasionally the attacks tend to disappear after the first year following cholecystectomy. This may be due to the fact that, as Judd and Mann have shown experimentally, the sphincter of Oddi tends to lose its tone and become incompetent after cholecystectomy (3). The loss of tone is however only functional since an appropriate stimulus, such as hydrochloric acid, may cause recurrence of the spasm (4). The reappearance of attacks of pain after a free

interval of five or six years following cholecystectomy may thus be explained.

It is difficult to account for the indigestion and constipation which so often accompanies gall bladder disease. It may be due in part to reflex spasm of the gastro-intestinal tract as a result of biliary pain. However since this dyspepsia tends to remain as a residual symptom in a large proportion of patients in whom pain has been relieved by cholecystectomy (5), other factors must be considered. One must always consider the possibility that gall bladder disease may be secondary to some primary dysfunction of the gastro-intestinal tract, made manifest by the various symptoms associated with dyspepsia. However there can be no doubt that a considerable number of patients with gall bladder disease are relieved of their dyspepsia after cholecystectomy. There may be, however, an other possible explanation for many of the gastro-intestinal symptoms associated with gall bladder disease. It is known that bile salts are of great importance in the process of digestion, especially of fat digestion. A point that has never been stressed sufficiently is the effect on the storage of bile salts if the gall bladder has been rendered functionally incompetent by disease or stones, or has been removed by operation. Normally the gall bladder contains about 75 cc. of bile, having a bile salt concentration of about 8%. Following the ingestion of food, the gall bladder pours into the intestine about six grams of bile salts in concentrated solution. If the gall bladder cannot empty or is absent there is present only a continuous flow of thin bile from the liver, containing a relatively dilute solution of bile salts. In addition, in the absence of the gall bladder as a storehouse, the body can keep in the entero-hepatic circulation only a small amount of bile salts, since there is probably no other place in the tissues where such a toxic substance could be stored in any quantity.

It is difficult to prove directly that there is a quantitative loss in the amount of bile salts in circulation in the body. Duodenal drainage removes only a portion of the biliary output. Recovery of bile by means of a fistula breaks up the entero-hepatic circulation and gives abnormal results. However, in a series of fistula bilcs analysed for bile acids, definite evidence was found indicating that many cases of chronic cholecys-

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titis have a bile acid concentration much lower than normal (6).

A more direct approach that would indicate that the dyspeptic symptoms and constipation in gall bladder disease might be due to partial lack of bile salts, would be to feed bile salts in adequate amount. The gall bladder contains about 75 cc. of bile (7) with a bile salt content of about 8% (8), and empties ordinarily about three times daily. A simple calculation indicates that during the course of daily digestion probably about 15 to 18 grams (225-270 grains) are poured into the intestinal tract. It would seem evident then that the dosage of bile salts formerly recommended and used (9, 10), would as a rule be inadequate, and yield rather unsatisfactory results. A series of cases in which large and more adequate amounts of bile salts were used was recently reported by Rosenak and Kohlstaedt (11).

In this presentation the results of treatment in 38 cases of various types of gall bladder disease are reported. The therapy was based on two principles: (1) a suitable diet and (2) administration of bile salts. It

TABLE I

Low carbohydrate, low fat, gall bladder diet

GENERAL RULES:

1. Eat lean meat, vegetables and fruit.
2. Drink plenty of water.
3. Eat three meals a day.
4. Do not eat between meals.

AVOID:

Fats—egg yolks, cream, butter, fat meats and fish, cream soups, fried foods, mayonnaise, oil, ice cream.

Carbohydrates—sugar, pastry, candy, potatoes, excess bread or crackers.

Meats—pork, duck, goose, any fat meat, gravy of all kinds.

Fish—salmon, sardines, herring, tuna fish, mackerel.

Vegetables—potatoes, corn, lima beans, fresh peas, kidney and navy beans.

USE:

Meats—(roast, grilled, boiled or baked). Lean roast beef, steaks, veal chop, veal cutlet, roast veal, lamb chops, roast lamb, sweetbreads, chicken.

Fish—Haddock, perch, smelts, cod, pike, halibut, lobster.

Vegetables—Asparagus, celery, cucumber, egg plant, lettuce, sour grass, spinach, squash, string beans, tomato, beets, carrots, onions, canned peas, turnips.

Desserts:

Fruits—Blackberries, canteloup, honeydew, grapefruit, peach, pineapple, strawberries, watermelon, apples, apricots, blueberries, pears, cherries, raspberries.

Pot cheese.

Jello, water ices.

DIET:

Break fast:

- 1 serving fresh fruit.
- 1 slice bread
- 1 cup coffee or tea with skimmed milk and no sugar.

Lunch and dinner:

- 1 serving soup (clear meat soup without fat, vegetable soup or tomato soup without cream or butter).
- 1 large serving lean meat or fish.
- 2 serving vegetables.
- 1 serving dessert, if desired.
- coffee or tea.

is well known that many people suffering from gall bladder disease have an intolerance for fats even after the gall bladder has been removed. In addition, since the gall bladder contracts actively following the ingestion of fats it would seem desirable to prevent such active contraction in a functioning gall bladder containing stones which could be forced into the cystic duct. Olive oil and oleic acid have been used in gall bladder therapy for many years on the theory that the frequent emptying of the viscous would prevent stasis and gall stone formation. It is notorious, however, that most patients with gall bladder disease cannot tolerate fatty meals. They are much more comfortable on a low fat diet; in addition it has been shown that the gall bladder will gradually empty even on a pure carbohydrate diet (12).

Whipple has shown experimentally that proteins stimulate the formation of bile salts, while carbohydrates tend to diminish their formation and also produce a thick viscid bile. Since most gall bladder patients are overweight, all these factors were considered in the elaboration of a low fat, low carbohydrate, high protein diet (Table I). An effort was made to produce an habitual gastro-intestinal rhythm, by requiring the patients to take their meals at regular hours and not to eat between meals.

On the principle that bile salts might be lacking in patients with gall bladder disease suffering from dyspeptic symptoms, from 15-60 grains of bile salts were administered daily. The therapeutic index taken to determine an adequate dosage was the control of constipation. All cathartics being stopped, the amount administered was gradually raised from 5 grains with each meal until bowel movements occurred at least once and not more than twice daily. As a rule about two weeks was necessary to stabilize the dosage. Once standardized, the amount each patient took daily could be maintained for many months. The average dose was from one to three 5 grain capsules at each meal.

In order to introduce the added bile salts at the optimum time to aid digestion, the capsules were administered in the midst of each meal. This allowed the bile salts to be mixed thoroughly with the food and prevented any tendency to gastric irritation. It was found that the administration of large amounts of plain bile salts often caused such gastric irritation. To overcome this an iron salt of ox bile acids in purified form was used.* This salt is insoluble in acid medium and accordingly does not dissolve in the stomach. As a result enteric coated capsules are not required for its administration. Once it is mixed with the alkaline duodenal contents it dissolves readily at the optimum point for emulsification and absorption of food.

Treatment was carried out on three groups of patients:

- (1) Cases with post-cholecystectomy symptoms.
- (2) Patients with functioning gall bladders containing stones (as determined by roentgen-ray visualization after dye administration).
- (3) Patients in whom the gall bladder could not be visualized.

Results:

Group 1—Patients with the post-cholecystectomy syndrome.

*This iron ox bile salt was at first made in Germany by Dr. G. H. B. but has since been purified by courtesy of the Lilly Co.

The results on 13 cases are tabulated (Table II). All patients except one (F.M.), were relieved of their dyspeptic symptoms and constipation. Six were relieved of their pain, and four showed marked diminution of their pain. One patient (A.R.) had persistent left upper quadrant pain without improvement. This was possibly due to pancreatitis. Another patient (R.S.) was found to be suffering from spondylitis and radiculitis, the pain of which was not relieved by our therapy. The third unrelieved case was a patient who apparently showed no improvement on 90 grains of bile salts daily. The persistence of the constipation led to the suspicion that she was not taking the medication. However this patient must be recorded as a complete failure of the treatment. It is noteworthy that treatment with mineral oil or such cathartics as Carlsbad salts, rhubarb and soda, or magnesium sulphate relieved the constipation, but neither the dyspeptic symptoms following meals nor the attacks of pain. In one patient (J.E.) the administration of atropin seemed to help in the control of attacks of pain.

Group 2—Cases with functioning gall bladders containing stones.

A group of 14 patients in whom the Graham-Cole radiographic examination revealed the presence of stones in a gall bladder capable of filling and emptying, (i.e., normal visualization and emptying after a fat meal) were put on a therapy of a low fat diet and bile salt administration (Table III). In all these cases

dyspepsia and constipation were relieved. In eight patients attacks of were also relieved. Four patients showed marked improvement in that the frequency and severity of pain attacks were reduced. Two of these patients, after 4 months therapy, developed an acute attack—one case (F.K.) after a fatty meal, and the other (F.A.) following a duodenal drainage in which olive oil was injected to obtain "B" bile.

One patient (C.P.) had marked gastric hyperacidity. Diet and bile salt therapy did not control the attacks of pain, which were apparently associated with the hyperacidity. It has been shown previously that application of acid to the papilla of Vater causes spasm of the common duct sphincter. This reflex spasm can be abolished by atropin (4). It seemed possible that in this case the frequent attacks of pain were due to recurrent spasm of the sphincter of Oddi. Accordingly alkalies and atropin were administered with marked relief of pain. Two other cases with hyperacidity (F.K. and M.R.) were well except for an occasional attack of pyrosis. In another patient (F.S.) in whom therapy failed, operation revealed a small stone lying in one of the valves of Heister in the cystic duct. The slightest flow of bile in either direction through the duct would tend to cause obstruction of the ball-valve type. In such cases only surgical intervention could lead to relief. We have since encountered two similar cases in whom failure of a short course of therapy led to the suspicion of the presence of a cystic duct stone. In both cases a stone was found in one of the valves of Heister at operation.

TABLE II
Cases with post-cholecystectomy symptoms

Name	Age	Sex	Symptoms			Bile Salt Therapy		Result of Therapy			Remarks
			Pain	Dyspepsia	Constipation	Daily Dosage Grains	Duration Therapy Months	Pain	Dyspepsia	Constipation	
B. E.	32	F	+	+	+	45	8	A	A	A	Attack of epigastric pain while on control period of mineral oil only.
J. E.		F	+	+	+	60	8	B	A	A	Nervous patient with coronary artery disease; atropin was helpful in therapy.
E. G.	56	F	+	+	+	15	18	A	B	A	Control period on rhubarb and soda only resulted in attacks of pain.
F. M.	34	F	+	+	+	90	2	C	C	C	Neither bile salts nor low fat diet had any effect on symptoms.
A. R.	43	F	+	+	+	30	6	C	A	A	Left upper quadrant pain prior to and after operation; pancreatitis (?).
S. S.	39	F	+	+	+	30	21	A	A	A	Control period on Carlsbad salts resulted in recurrence of symptoms.
G. S.	33	F	+	+	+	15	12	B	A	A	Well for 10 months; attacks of pain and diarrhea then recurred.
R. S.	54	F	+	+	+	90	4	C	A	A	Pain was found to be due spondylitis and radiculitis.
R. N.	53	F	0	+	+	30	4	A	A	A	
R. J.	45	F	+	+	+	30	1	B	A	A	Pain was in left upper quadrant and recurred after one month's treatment.
T. G.	38	F	+	+	+	30	3	B	A	A	Achlorhydria present; functioning gall bladder without stones removed at operation.
J. S.	47	F	+	+	+	15	6	A	A	A	Has continuous dull ache in R.U.Q. due to adhesions.
F. L.	59	F	+	+	+	20	3	A	A	A	Control period on magnesium sulphate resulted in recurrence of symptoms.

Notes:
A—Relieved B—Improved C—Unchanged

The impression was gained that in patients in whom therapy was stopped either deliberately or due to a temporary lack of a supply of bile salts, the symptoms both of pain and dyspepsia tended to recur. Five patients in whom constipation was overcome by administration of magnesium sulphate, Carlsbad salts, or rhubarb and soda, during a control period, were however, not relieved of dyspepsia or pain.

Group 3—Cases with non-visualized gall bladders.

A series of 11 patients in whom the gall bladder did not visualize after dye administration, were also treated by diet and bile salt therapy (Table IV). The presence or absence of stones could not be determined. Dyspepsia and constipation were overcome in all cases. Eight patients were rendered free of pain, although in one case (R.M.) bile salt therapy had to be stopped when an attack of mucous colitis recurred. Two patients showed marked improvement in that the frequency and severity of attacks of pain were reduced. One of these patients (K.H.) had marked gastric hyperacidity, while in another patient (F.B.) repeated dietary indiscretions resulted in many attacks of pain.

DISCUSSION

Our experience indicates that the majority of patients who suffer from pain and dyspepsia after cholecystectomy can be relieved by a fat free diet and by an adequate intake of bile salts. Certain exceptions, however, must be carefully noted. If a choledochal stone is present, the increased flow of bile following bile salt administration results in accentuation of symptoms or even the appearance of jaundice. Such a condition was noted in two patients. In one of these, previously reported (13), bile salt therapy increased the frequency of attacks. At operation, a small stone was found in the common bile duct, although no jaundice was ever present. In the other patient bile salt therapy resulted in the appearance of jaundice. At operation two choledochal stones were found.

Any condition, such as partial stricture, malignancy, or chronic pancreatitis which would diminish the diameter of the common bile duct, could cause increase in symptoms on bile salt therapy. In one case jaundice developed soon after administration of bile salts. At operation malignancy of the common bile duct was

TABLE III
Cases with functioning gall bladders containing stones

Name	Age	Sex	Symptoms				Bile Salt Therapy		Result of Therapy			Remarks
			Duration Symptoms	Pain	Dyspepsia	Constipation	Daily Dosage Grains	Duration Therapy Months	Pain	Dyspepsia	Constipation	
S. S.	59	M	20 years	++	+	+	45	6	B	A	A	Coronary sclerosis.
D. F.	33	F	6 years	+	+	+	25	11	B	A	A	Hypertension with cardiac failure.
L. H.	52	F	20 years	+	+	+	30	6	A	A	A	Attacks on Carlsbad salt therapy.
D. K.	34	F	12 years	++	+	0	10	6	A	A	A	Attacks occurred on stoppage of therapy.
M. K.	35	F	6 months	++	+	+	40	10	B	A	A	Attack after fatty meal, required operation. hyperacidity; Carlsbad salts or rhubarb and soda control periods caused recurrence of dyspepsia
C. P.	38	F	6 years	+	+	+	45	4	C	A	A	Hyperacidity. Atropin and alkalies effective.
R. W.	46	F	1 year	+	+	+	30	17	A	A	A	Attack following 5 day stoppage bile salt; on mar. sulphate control periods recurrence of pain and dyspepsia
F. A.	26	F	2 years	+	+	+	30	4	B	A	A	Acute cholecystitis after olive oil
F. S.	37	M	6 months	+	+	+	15	4	C	A	A	Operation revealed cystic duct stone.
H. S.	42	F	3 years	+	+	+	30	6	A	A	A	Symptoms occurred after cessation of therapy.
M. M.	38	F	1 year	++	+	+	20	11	A	A	A	During rhubarb and soda control period dyspepsia reappeared.
M. G.	40	F	6 years	+	+	+	30	6	A	A	A	Persistent lactacids which patient had previously disappeared after therapy.
M. G.	62	F	5 years	+	+	+	20	1½	A	A	A	Severe attacks of pain after dietary indiscretions.
M. R.	56	F	5 years	+	+	+	20	7	A	A	A	Hyperacidity; occasional slight cramps relieved by alkalies

Notes:
A—Relieved B—Improved C—Unchanged

found, resulting in incomplete stricture. The increased flow of bile resulted in obstruction and jaundice. It follows therefore that bile salt administration may prove useful as a test for the presence of partial organic obstruction.

The presence of gastric hyperacidity renders treatment very difficult. In such cases the frequent attacks of pain seem to be due to the recurrent spasm of the sphincter of Oddi. The addition of atropin and alkalies to the therapy is of great assistance. The neurotic patient is also difficult to treat, since any emotional upset brings on an attack of pain. This is apparently due to a spastic condition of the gastro-intestinal tract which involves, among other sphincters, the common duct sphincter as well.

It is difficult to explain the disappearance or reduction in the number of attacks of pain when bile salts are administered. It would seem that the increased flow of bile from the liver, the disappearance of the difficulty in digestion and the improvement in intestinal peristaltic action all tend to eliminate the tendency to gastro-intestinal spasm. In support of this it has often been noted that the relief of constipation only by the ordinary saline cathartics is occasionally of some assistance in the improvement of painful symptoms.

The cases in whom the gall bladder was still present, are presented not primarily to recommend this form of therapy as the preferred treatment for gall bladder disease, but to point out that these patients may be treated satisfactorily medically. This therapy is especially important in old and debilitated people, in cases with associated cardiac disease, or other con-

ditions where operation is dangerous, and also in people who refuse operation.

The removal of a functioning gall bladder containing a few stones should be deprecated on general physiologic principles, since its important function as a storehouse for bile salts would be lost. Medical therapy should be attempted before operation is advised. However there is often great difficulty in keeping such patients on a fat free diet to prevent active contraction of the gall bladder. Certainly in many cases, especially where a small stone is present in the cystic duct, no diet can be rigid enough to prevent attacks of pain due to recurrent impaction of a stone.

In addition to these difficulties, the problem is raised whether it is not preferable to remove a gall bladder containing stones as soon as the diagnosis is made, rather than to wait for more serious complications to ensue later in life. The question cannot be discussed here. The point we should like to stress is that the treatment of patients suffering from gall bladder disease cannot be condensed to a few rule of thumb directions. Our experience, however, indicates that if one keeps constantly in mind the known physiologic principles of the biliary and gastro-intestinal tracts, one can achieve considerable success in the therapy of gall bladder disease.

SUMMARY

(1) 3 groups of patients with gall bladder disease are described.

(2) The use of a low fat diet and large amounts of bile salts is advocated in the treatment of these cases.

(3) In the group (13 cases) with the type of post-cholecystectomy syndrome not due to organic obstruc-

TABLE IV
Cases with non-visualized gall bladders

Name	Age	Sex	Duration Symptoms	Symptoms			Bile Salt Therapy		Result of Therapy			Remarks
				Pain	Dys- pepsia	Consti- pation	Daily Dosage Grains	Duration Therapy Months	Pain	Dys- pepsia	Consti- pation	
P. Z.	57	F	10 years	+	+	+	30	6	A	A	A	Diabetic; occasional slight epigastric distress on therapy.
F. B.	58	F	10 years	++	+	+	45	4	C	B	A	Repeated dietary indiscretions brought on attacks.
R. M.	62	F	20 years	+	+	+	45	3	A	A	A	Mucous colitis 15 yrs. Bile salts therapy stopped on recurrence of symptoms.
G. K.	40	F	3 years	+	+	0	15		B	A	A	Cholecystostomy 2 yrs. ago; recurrence of attacks 3 yrs.
K. H.	42	F	12 years	+	+	+	25	9	B	A	A	Hyperacidity; on mag. sulphate only constipation cured.
E. B.	49	F	3 years	+	+	+	30	8	A	A	A	Recurrence of symptoms when therapy stopped.
A. K.	25	M	10 years	+	+	+	25	7	A	A	A	Attack of severe pain following fatty meal.
P. S.	72	M	15 years	+	+	+	55	10	A	A	A	Asthmatic; well as long as bile salts taken.
S. H.	43	F	10 years	++	+	+	25	13	A	A	A	Recurrence of severe dyspepsia on Carlsbad salts control periods.
M. G.	40	F	2 years	+	+	+	35		A	A	A	
M. H.	44	M	8 years	++	+	+	15	3	A	A	A	

Not
A—Believed B—Improved C—Unchanged

tion, relief was obtained in most of the cases with this form of therapy.

(4) In two other groups, i.e., those with stones and normally functioning gall bladders (14 cases) and those with chronic gall bladder disease in whom the gall bladder failed to visualize (11 cases) considerable

relief from symptoms was also obtained.

(5) In the cases in whom gastric hyperacidity was present atropin and alkalies were helpful adjuvants in the therapy.

(6) In view of these results, the use of this mode of therapy in a larger group of cases seems advisable.

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The Symptomatology of Gastritis

By

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THE interest of most workers in the field of gastric pathology has been directed toward classification and possible etiological relationship of various conditions, one to another. The result has been a considerable literature concerned with histologic study of postmortem or resected material, and objective description of appearance at operation, of necropsy material, radiography and gastroscopy. There are certain wide discrepancies apparent—largely due to differences of interpretation of actually identical conditions and the drawing of unwarranted conclusions from limited methods or material. There is as yet, for instance, no common definitive basis upon which to explain gastroscopic pictures, roentgenographic "relief technic" films, formalized autopsy material, surgically resected tissue or the various phenomena of gastric secretions. Only isolated and casual attempts have been made to translate gastroscopic discoveries in terms of clinical manifestations or symptomatology, particularly with reference to gastritis.

Schindler (1) has recently stated that "all authors who have made gastroscopic examinations in many cases of chronic gastritis have agreed that the symptomatology is so vague that neither diagnosis nor classification on a symptomatologic basis is possible, 'that the most any one can ascertain of the patient's symptoms are anorexia, pressure in epigastrium, disinclination to work, and occasionally severe pain if severe erosions or hemorrhage of mucosa be present, and concludes that 'at this time' diagnosis of chronic gastritis on basis of symptoms is impossible." It was Schindler who in 1922 (2) on the basis of gastroscopic studies pointed out the frequency of chronic gastritis; herein was set forth the different forms of gastritis and in a subsequent review (3) of his material an attempt was made to evaluate symptoms in relation to these various forms.

Gutzeit (4) also says that the clinical diagnosis of gastritis is difficult because gastritis may take on nearly all the symptoms of the various abdominal diseases. He could not find any correlation with acid values. Many times he found various nervous and traumatic factors in the history (he probably did not segregate the psychoneuroses), and altogether he seems inclined to think, because of the confusion of symptoms, that gastritis may be a part of a general gastro-enterocolitis. In spite of these conclusions, from cases cited by him (5) the usual history seems to be that of pain or some kind of distress immediately after meals with loss of appetite—often weight loss—and irregularity of bowels (constipation or diarrhea) occurring at intervals over a long period of years. Often the pain occurred late after meals as in ulcer, but was seldom as well localized. Occasional belching with bitter or sour eructation occurred.

Moutier (6) precedes his discussion of gastritis by recognizing "the difficulty of establishing a relationship between the microscopic appearance, the histological lesions, the secretory values, and the clinical pictures." He attempts to establish pictures of primary gastritis by classification according to probable etiology. For instance, in acute gastritis he recognizes two forms: "Toxic-infectious" and "Chemical." Of the clinical forms of chronic gastritis, he lists: "Toxic" (lead and alcohol) and dyspeptic, where the symptoms occur either early or late after meals, with eructation, bloating, pyrosis, somnolence, fatigue and headache. The pain may be epigastric or umbilical in location, or diffuse. When these dyspeptic symptoms are produced by superficial and atrophic forms of gastritis the distress is present with or immediately after meals, the distress in the hypertrophic form usually is late and may be more severe and cramplike. The ulcerative forms are likely to have continuous pain, but night pain is rare with any form. He concludes, as he began, by saying that up to the present it is impossible to

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define syndromes which will include clinical, laboratory, pathological and gastroscopic data.

Benedict (7) in a study of forty cases of gastritis, lists the symptoms epigastric pain or distress, nausea, vomiting, eructation, heart-burn, gas, anorexia, fullness, hematemesis and melena, of which epigastric pain and distress are the most constant complaints, with gas, nausea and vomiting frequent, and hematemesis and melena not uncommon. He emphasizes evidences of hemorrhage either gross or occult as strongly indicative of gastritis when X-ray reports have been negative. About one-half of his gastritis cases have shown some evidences, clinically, of hemorrhage.

In the cases which Faber (8) describes of rather severe erosive gastritis, the history was that commonly considered characteristic of peptic ulcer, namely, late post cibum pain, night pain, food relief, occult hemorrhage, periodicity and chronicity. He found in these severe gastritis cases further "ulcer symptoms," i.e., hyperacidity, hypersecretion, nausea, vomiting, various degrees of retention and pylorospasm. The similarity between symptoms of gastritis and ulcer is explicable on the assumption that either locally or generally inflamed mucous membrane responds to increased peristalsis (irritable hypermotility, spasm or hunger contractions) with sensation of pain.

Katsch (9) has classified the symptoms of gastritis into six groups:

1. Sensitive stomach—"acidism," epigastric burning, heart burn, eructation.
2. Pyloric syndrome—includes postcibum pain, nausea and vomiting.
3. Dyspeptic and intestinal symptoms—diarrhea, constipation, flatulence, anorexia, qualitative and quantitative dyspepsia.
4. Anemic—hypochromic type (achlorhydria).
5. Hemorrhagic evidences.
6. Acutely painful variety—often simulating perforation of a viscus. But he also warns that only in clear-cut cases have gastroscopic findings and the clinical picture been absolutely related.

Eusterman (10) has lately surveyed the question of gastritis from the clinical standpoint, with laudable conservatism. He rightfully insists that acute forms of gastritis due to ingestion of poisonous substances, phlegmonous gastritis, syphilitic and anemic (pernicious and hypochromic) gastritis have long been recognized. Secondary forms, such as found associated with hepatic, cardiac, and renal diseases, diabetes, tuberculosis and other conditions should not be confused with primary gastritis, although pathologically they may show similar congestive, atrophic, hypertrophic erosive, hemorrhagic or ulcerative changes. He then lists ten cases of primary gastritis from which tissue was removed at time of operation. All of these cases had had a positive roentgen diagnosis of some gastric lesion and had been assumed clinically to be ulcer (5), cancer (3), tumor (1) and polyp (1). In nine cases the pathologic diagnosis was some form of gastritis and in one case duodenitis. The symptoms varied somewhat, but in order of frequency were about as follows: Vomiting, nausea, various degrees of epigastric distress, fullness, or pain, (usually at intervals after meals and occasionally with food relief, loss of weight, anorexia, sour stomach, flatulence and weakness.

Henning (11), Von Bergman (12), Korbach (13), Schloss (14) and many others have written in about the same way concerning symptomatology. There seems to be a certain uniformity in their clinical observations. All agree that the so-called pyloric syndrome may be activated by the more severe grades of gastritis. For the less severe grades of gastritis apparently some type of epigastric distress, either immediately following or long after a meal with or without food relief, is expected. In more chronic forms, continuous distress is more likely. Nausea, vomiting, and some evidence of bleeding are quite common, together with anorexia and possibly loss of weight. These symptoms may be accompanied by pyrosis or intestinal symptoms of flatulence, diarrhea or constipation. Most of the authors mention the lack of any localizing findings on physical examination of the abdomen. That is, there is seldom a point of maximum tenderness, the distress being rather diffuse in epigastrium or at least somewhere above the navel.

Our material is composed of 375 gastroscopies, among which 112 individual diagnoses of primary gastritis were made.

All cases in which gastritis was seen to be a condition secondary to, or at least accompanying, other disease were eliminated. Consequently no cases of duodenal ulcer, gastric ulcer, carcinoma, pernicious anemia or gastric operation were included. Although there may be, and usually is, some type of gastritis present with most of these pathologic states, the major signs and symptoms would be presumptively those of the primary condition. We are attempting, in the first place, to determine whether or not gastritis produces symptoms, and if so, whether they are sufficiently peculiar to the condition to have diagnostic value.

In our gastroscopic diagnosis we have followed the simple classification of Schindler (1): superficial catarrhal gastritis; atrophic gastritis and hypertrophic gastritis. We have found, as he pointed out, that the first two conditions seem to be related inasmuch as some cases showed evidences of superficial gastritis together with atrophic changes. In the hypertrophic group various forms were recognized as hemorrhagic, ulcerative, erosive and exudative.

The criteria for superficial gastritis are excess of mucous secretion, usually with flecks adherent to the membrane, together with evidences of congestion, small hemorrhages, occasional edema and hypersecretion. In atrophic gastritis, the mucosa is recognized as being thinner, with visible blood vessels and grey or green-gray areas. In hypertrophic gastritis the mucosa is more red than normal, thicker, with irregular granular, cobblestone, mosaic or pavement appearance, and showing usually also hemorrhagic areas, erosions, ulcerations, or exudate. The superficial and hypertrophic forms tended to have hypermotility or increased activity (contractures or spasms), intolerance to air and other evidences of increased gastric irritability.

The symptomatology of superficial catarrhal gastritis is apparently that of pain immediately after meals, either not relieved by food or aggravated by it. The history is likely to be of short duration and the patients are young (20-40). The X-ray of the GI tract is usually negative, as is the physical examination.

Two cases may be briefly mentioned indicating modification of this type of case. The first is that of an alcoholic with a very typical "ulcer" history over a

long period of time with repeated attacks of hematemesis. The mucosa was markedly congested with great excess of mucus. The other was a young woman with nausea and vomiting as the outstanding symptoms, and was found to have discrete aphthous lesions in the antrum region. These disappeared and the mucosa returned to a normal appearance in about five weeks.

In addition to neuter catarrhal and exudative changes, in many cases atrophy of the mucosa was seen and patients showing such changes have longer duration of history and are of a somewhat older age group (40-60). Their stories are pretty generally that of constant "indigestion," pain of dull character and diffuse upper abdominal location, sour stomach, gas and belching. They have had occasional temporary relief by change of diet. Sore mouth or dysphagia often initiated the more acute exacerbations. X-ray examination in these patients is uniformly negative.

It is a question whether these patients have a primary atrophic mucosa which is so easily irritated that it is subject to repeated acute inflammatory reactions, or whether as a result of such recurrent insults the mucosa finally becomes atrophic. In some patients, who complain that their stomachs have always given them trouble, the first idea is probably correct. We need not discuss whether they were born with a constitutionally defective mucosa, or whether it became so in very early life as a result of childhood infection (Faber (8)). In other patients the history is more limited in time, and more definite as to onset of symptoms, so that one may be allowed to predicate the second of the above theories, which is, in fact, the opinion of most gastroscopists in this matter.

ATROPHIC GASTRITIS

The symptomatology of chronic atrophic gastritis is that of upper abdominal discomfort of a pressure type, often called gas by the patient and accompanied by belching, nausea and vomiting. The distress comes on immediately post cibum and is definitely not relieved by food or medicine taken. Loss of appetite with loss of weight and anemia is often present. Sore mouth or tongue is frequent. These patients suggest the possibilities of malignancy or pernicious anemia. Almost without exception there is a complete absence of HCl in gastric secretion. The age group is again somewhat older (40-60) and the duration of symptoms is generally long (10 years or "all the life"), persistent and constant.

It is at times doubtful whether or not some of the cases mentioned in the previous paragraph should be included under the classification of atrophic gastritis with acute exacerbations, in which case the history is at least over a period, intermittent and the symptoms are somewhat sharper as to painful experiences. Then there are a few patients seen with atrophic mucosa, complete achlorhydria to histamine, who never had had any gastric complaints. The mucosa is certainly atrophic, but is it gastritis? At any rate, a sufficient number of patients with atrophy of the gastric mucosa are seen, with or without more acute inflammatory changes who do have the symptoms mentioned above so that a fairly clear concept of atrophic gastritis has been acquired.

HYPERTROPHIC GASTRITIS

In this group the symptoms are very frequently those characteristic of the ulcer syndrome. But on

close questioning, the patients usually complain that they have distress immediately on eating as well as sometime afterwards, and food or alkali case is not invariable. Many are simply not relieved by food or soda and a few are aggravated thereby. The pain is not discretely circumscribed, does not radiate and rarely occurs at night, contrasted with continuous discomfort of atrophic gastritis; there is periodicity or remissions in the hypertrophic forms, but the total duration of symptoms is not as long. Nausea and vomiting, with relief by vomiting, are much more prevalent than in the ulcer group.

Vomiting in gastritis is the reaction of an intensely and generally irritated mucosa and hence accompanied by pain, nausea and retching, comes soon after meals and gives relief. Vomiting in ulcer is usually to relieve retention caused by obstructive inflammation, scar or spasm at or near the pylorus.

The age range is wide (20-60 years). The acid values are quite variable, some achylia, most hyperacid, and many normal or anacid. The X-ray gastric study usually results in a diagnosis of some irregularities of ulcer type, either single or multiple; some have been diagnosed gastritis when the mucosal relief seemed characteristic. Occasionally a single niche characteristic of gastric ulcer is described, which when viewed gastroscopically is seen to be only one of multiple ulcerations. The radiologist often indicated hyper-rugation and many times found the stomach entirely negative.

The impression is very strong that the time spent in carefully developing, classifying and analyzing many so-called ulcer histories will be rewarded. The tendency to accept the patient's original story at its face value or even to simplify it in terms of conventional forms is too prevalent. When a patient says that he has pain after meals, so well drilled is the historian in "ulcer phraseology" that he many times assumes "food case" without asking. Our experience has been that if the patient be explicitly quizzed on the exact relationship of his distress and means he has taken for his comfort, that a deviation from the classical form will be elicited which will indicate at least the probability of a diagnosis other than ulcer. When, after very careful questioning, the story seems to be that usually associated with ulcer—namely the food-pain-food-case sequence—the gastroscopic examination has revealed the ulcerative form of gastritis, or more rarely hypertrophic mucosa with rather deep sub-mucosal hemorrhages. These cases have not been found as commonly, however, as the type showing hypertrophic changes with exudation, superficial hemorrhages and erosions, which give the histories as analyzed above. There are, however, some cases whose history is modified from that of true ulcer, as suggested above, but in whom a typical round or peptic ulcer without generalized gastritis is found on gastroscopic examination; which emphasizes the necessity for such examination in all patients with any sort of gastric complaints in order that a correct diagnosis may be made.

In order that a control group might be contrasted, the records of patients in whom negative or normal gastroscopic findings were recorded were examined. Some of these examinations were done because the clinician wished to eliminate stomach as possible source of anemia, because of laboratory report of blood in stool, or for some other reason, when no gastric

history at all was present. In other cases recorded as normal a diagnosis of some other intra-abdominal disease was subsequently made. These patients were eliminated from present consideration. The residual cases were almost without exception psychoneurotic individuals with innumerable somatic complaints, of which the gastric symptoms were only a part. Several had migraine, some were air-swallowers, a few had pylorospasm, some with history of vomiting and some with a slight degree of cardiospasm. But there was never an unequivocal history of only gastric disorder. The reference for gastroscopic examination was usually made by the clinician in full recognition of the functional character of the complaint, but because he wished a definite opinion upon which to base his discussion of negative findings with the patient. The essential fact is, therefore, that the history of the patient whose gastric mucosa is found to be normal is not likely to be confused with that of one showing definite changes. He either has no gastric symptoms at all, or such gastro-intestinal symptoms as he does present are merely a part of a general psychoneurotic galaxy at the least explicable by globus, aerophagia, cardiospasm, pylorospasm or spastic bowel disturbances. An occasional patient with a well developed psychoneurosis is found by gastroscopy to have an atrophic gastric mucosa; just what the relationship is, is doubtful. Both Schindler (15) and (Moutier (6) have commented upon this condition.

SUMMARY

Superficial Catarrhal Gastritis occurs in young people, has a short history characterized by epigastric distress immediately on eating, not relieved by further food or alkali ingestion. This type of gastritis, if subject to frequent exacerbations, probably results in permanent atrophic changes and eventually occasions the symptoms of chronic atrophic gastritis.

In well established *atrophic gastritis* the history is of persistent, constant upper abdominal distress of pressure type, not relieved by food or alkali, with anorexia and nausea, and occasional vomiting. The duration is many years. The patients are in the 4th, 5th and 6th decade, and have often lost weight and become anemic, hence to be differentiated from malignancy or pernicious anemia; they may be subject to acute exacerbations, often with sore mouth and tongue.

The *hypertrophic gastric* patients have epigastric pain, either immediately post cibum or at an interval thereafter, sometimes with food or alkali relief, but more often being not relieved or aggravated thereby and with a pronounced tendency to nausea and vomiting, the latter giving relief. The history is of long duration with periods of remission. The type of pain is burning or gnawing, or a dull ache, but does not radiate nor occur at night and is diffuse in upper abdomen.

The X-ray findings in the superficial and atrophic

forms of gastritis are negative, while in the hypertrophic forms they are equivocal, indeterminate, or show ulcer niche types of defects, often multiple. Occasionally the diagnosis of gastritis has been made, usually in the hypertrophic type by changes in mucosal pattern.

There is no diagnostic aid from the evaluation of degrees of acidity of the gastric secretions in the superficial forms; the atrophic forms are distinctly achlorhydric, while the hypertrophic type may be achylie, anacid, hypo or hyper-acid, with a preponderant number of the last.

Evidences of gastric hemorrhage, either hematemesis, or melena has been found with all forms of gastritis, possibly more frequently with the hypertrophic types. We agree with Benedict therefore, that hemorrhagic evidences are strongly indicative of gastritis if another responsible lesion has not been demonstrated.

CONCLUSION

The impressions gained from a survey of the literature previously given seems to be borne out by this study. That is, any stable patient without psychoneurotic stigmata who has a definite consistent story of some type of gastric distress and in whom neither X-ray nor physical examination has revealed characteristic findings, may be given a presumptive diagnosis of gastritis. Gastroscopy in this type of patient is definitely indicated, and if done, will probably reveal some change of the gastric mucosa. If the history has been continuous over a considerable period and has consisted of dull, heavy pressure discomfort, unrelieved by anything he has been able to do, resulting in anorexia and loss of weight and anemia, he may be suspected of having the atrophic form, particularly if he has achlorhydria. If the history has been of long duration but with periodic remissions, characterized by pain occurring sometime in the digestive cycle, either not relieved or aggravated by food and relieved by vomiting, non-radiating and diffuse, he may be suffering from the hypertrophic form of gastritis, particularly if X-ray reports have been indeterminate, negative or uncertain. If the history has been quite typical for ulcer, but the X-ray examination has been negative or shown questionable defects, he may have a gastric ulcer or ulcerative, erosive or hemorrhagic gastritis. Finally, critical judgment of the above observations and analyses leads inevitably to the opinion that gastroscopy should be employed as an adjunctive method of diagnosis of gastric conditions. Since submitting this article for publication, a total of 475 gastroscopic examinations has been done, with a diagnosis of primary gastritis made in 134 incidents. A careful survey of these patients, as to symptomatology, has not changed the opinions which follow in any important particular.

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Esophageal Varices in Portal Hypertension*

Pathogenesis and Diagnosis by Roentgenography

By

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IN the consideration of the patient who has been vomiting blood, only too often is scant attention paid to the possibility of the hematemesis being caused by lesions other than bleeding peptic ulcer. Lesions of the esophagus ranging from ulcer to cancer, gastritis, gastric carcinoma, gall bladder disease, blood dyscrasias, certain acute febrile diseases, and, above all, the group of cases associated with portal hypertension (portal and unclassified hepatic cirrhosis, splenic or portal thrombosis, splenic anemia and Banti's syndrome, schistosomiasis mansoni) may be responsible for hematemesis. Bulmer (1), noting 67 deaths directly due to gastro-intestinal hemorrhage, found nine that were caused by hepatic cirrhosis or portal thrombosis. Rivers and Wilbur (2) found 4 out of 27 deaths to be due to the same causes and found cirrhosis of the liver or splenic anemia to account for 5.1% of 668 cases which were admitted to the Mayo Clinic with hematemesis as chief complaint. Viewed from the standpoint of the cirrhosis, the importance of hematemesis becomes clear when it is realized that about 25% of patients with this disease have hemorrhages (3). McIndoe (4), analyzing 26 cases of advanced cirrhosis, found that 50% died of gastro-intestinal hemorrhage. Blumenau (5) found that 19% of 126 cases of portal cirrhosis died from vascular lesions. Since the life expectancy of the average patient with portal cirrhosis has been increased (4) since the introduction of newer medical treatments such as the use of mercurial diuretics and high carbohydrate diets, there has been a striking increase in fatal lesions of the vascular tree. There is every reason to expect this trend to continue.

PATHOGENESIS

A brief consideration of the pathogenesis of varices of the esophagus is essential for a better understanding of their production and early diagnosis. In portal hypertension (6), blood which normally flows freely through the portal veins is dammed back into its tributaries and through new or little used collaterals into the systemic circulation. The anastomosis in the lower third of the esophagus is composed, on the portal side, of vessels which are found in the cardiac end of the stomach. In turn, these are formed by two veins or groups of veins. Most important is the coronary vein (may be multiple) which normally runs along the lesser curvature of the stomach, anastomoses with the pyloric veins and enters into the portal vein directly behind the superior part of the duodenum. The

coronary vein drains the lower part of the esophagus, the cardia, and anterior and posterior surfaces of the stomach.

The second group consists of the left gastroepiploic vein and the short gastric veins which run between the spleen and the superior half of the greater curvature, anastomosing with branches of the coronary vein and joining in the formation of a cardiac rete or plexus of veins. It is this second group of vessels which may primarily involve in splenic disease without notable portal obstruction. The diagram (Fig. 1) illustrates these anastomoses and indicates as well the connections between the esophageal network and the systemic circulation. It will be noted that for a short distance just above the cardia, there exist small longitudinal venules with cross anastomoses. Above this point is a rich network, the usual location of clinically significant varices.

At the cardia, the veins are strongly supported by a thick muscularis interna and an adherent mucosa bound down to the submucosa by strong interlacing fibers and connective tissue. Above this point, however, the rich venous anastomosis of the submucosa is very poorly supported by loose connective tissue, hence an ideal site for the formation of varicosities, especially with the superimposed aspirating effect of negative intrathoracic pressure.

Since medical treatment has been essentially unsuccessful in the management of the bleeding of portal hypertension, surgical intervention based on early diagnosis offers the most hope and will probably often be the method of choice. As McIndoe (4), Mandel and Marcus, Kegaries (6), Walters (7), Rousselot (8) and others have indicated, the following surgical procedures have been recommended at one time or another. 1. Cauterization: a direct attack made through the esophagoscope which has met with little success. 2. Ligation of the coronary veins: theoretically excellent and sometimes quite simple but not always possible. 3. Ligation of the vasa brevia, may be combined with the second or fourth method or both. Failure to ligate these veins properly may account for recurrent hemorrhage. 4. Splenectomy about which numerous articles have been written. It is said to reduce the portal blood by 20% (9). Burton-Opitz (10) found that in the dog 21% of the portal blood comes from the spleen. Simonds (11) has outlined the objections to splenectomy. 5. Increase of collateral circulation: production of Eck fistula (not feasible clinically) or the Talma-Morrison operation. The latter, occasionally brilliantly successful, has usually not been satisfactory. It may be performed after completing ligation of the coronary veins.

There is reason to believe, therefore, that surgical

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Intervention can offer some hope of increasing the comfort and prolonging the life of patients with esophageal varices but progress will be difficult until earlier diagnosis is made possible. X-ray diagnosis has recently received much attention in the literature and we have found it to be extremely useful in the early establishment of the presence of esophageal varices.

X-RAY VISUALIZATION

X-ray observations vary greatly with the anatomical stage of the disease. Oppenheimer (12), in a recent excellent comprehensive study of a large series, points out three groups: 1. The early stage, marked by a slight and diffuse venous congestion, resulting in moderate broadening of the rugae of the lower part of the esophagus. 2. Beginning dilatation of larger individual veins which emerge from the submucosa into the mucosal relief, marked by small rounded defects seen in the relief of the lower fifth of the tube. 3. Generalized enlargement of numerous veins which encroach upon the mucosa in which period the typical vermiform negative shadows predominate.

Since varices, as Oppenheimer points out, are compressible anatomic formations, various factors may influence their filling. Definite variations in their character are produced by peristalsis, especially stripping, and by mechanical pressure as of a large bolus or tumor formation. These factors force blood into the lower vessels. In early portal congestion, the blood can still pass into the abdominal veins. Later, it is expressed from the upper varices into the lower ones, overfilling the latter.

At the beginning, this mechanism makes varices invisible and the early congestion is frequently recognizable clinically on positive X-ray signs only. In advanced stages, only a part of the whole extent is visualized and roentgenograms generally do no more

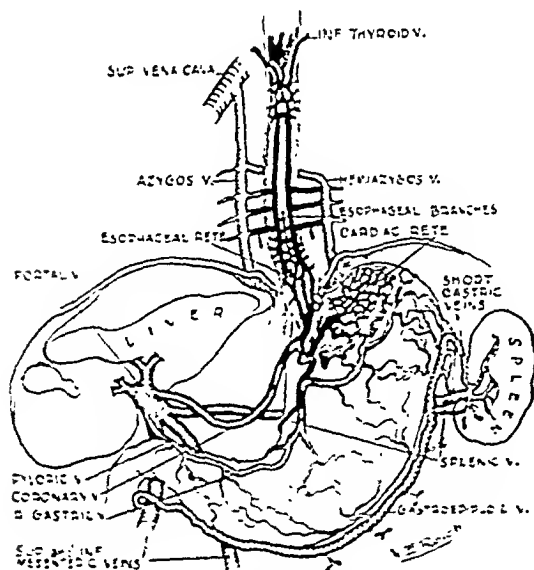


Fig. 1. Formation of varices in the esophagus and cardia. Note that the upper third of the stomach and esophagus has been exposed by removal of the anterior wall (Modified from Brdiczka and Tschakert (12B) and Kegaries (6)).

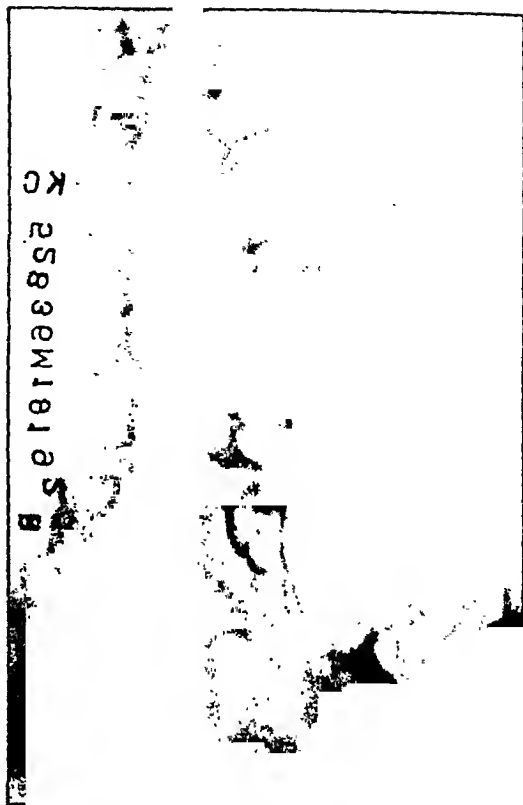


Fig. 2. X-ray of Barium-filled Esophagus illustrating Esophageal Varices.

than confirm the clinical diagnosis. It is necessary, therefore, to demonstrate the mucosal relief when unaltered by peristalsis or mechanical compression.

Optimal visualization, according to Oppenheimer, depends upon several factors. The films should be exposed during forced inspiration as esophageal varices form best at this moment. They are best seen during the short interval between swallowing and stripping. The retardation of the passage through the esophagus varies between a few seconds in early congestion and several hours in terminal stages with superimposed cardiospasm. It is often due only to mechanical obstruction by the varicose mass but it must be remembered that in both the early and terminal stages various functional disturbances affecting the cardia, such as cardiospasm, also produce esophageal stasis. It is important to differentiate esophageal carcinoma which may occasionally produce a similar X-ray picture, by careful history, physical examination and, if necessary, by esophagoscopy. As will be pointed out later, the distinction can also be made on purely roentgenological grounds.

X-ray visualization has distinct advantages over direct visualization through the esophagoscope for several reasons. Esophagoscopy (13) is a highly specialized procedure to be attempted only by those with adequate experience. It may not even be available in smaller institutions and it is definitely not an office procedure. The possibility of direct trauma to a

varix with fatal hemorrhage or perforation of the esophageal wall is an ever-present danger; or, as previously described, mechanical pressure may express blood from upper varices to lower ones, overfilling the latter to the bursting point. In an earlier stage, blood may be expressed from the venous bed with temporary disappearance of the affected area and consequently may pass unnoticed. The production of inflammatory complications, from a transient throat soreness to an acute esophagitis or even mediastinitis is possible. Finally, the consideration of refusal of an operative procedure on the part of the patient may be decisive.

On the other hand, roentgenograms are usually available everywhere, present the typical appearances, are simple of application and not attendant with any of the previously mentioned objections.

The differential diagnosis by X-ray includes first, the differentiation from food particles. When the latter cast suspicious shadows, repetition of the examination after thorough evacuation of the esophagus will fail to reveal lesions. The presence of polypi can be ruled by the rapid passage of the barium and the absence of obstruction in proportion to the degree of protrusion. New growth may be ruled out by the softness of the esophageal wall and its elasticity which appears unimpaired. There is not enough constriction and irregularity of the wall to resemble syphilis. Finally, cardiospasm may be ruled out by the absence of the smooth esophageal wall so characteristic of that condition.

TYPICAL CASE HISTORY

M. M., 35, male, American of Italian descent, was admitted to the Kings County Hospital, vomiting blood. He had had a continuous hematemesis since three that morning when he had been awakened by nausea and a cold sweat. Gastro-intestinal history: no constipation, diarrhea, or hemorrhoids. He had been a moderate drinker of spirits for years. One year ago he had been admitted to the hospital for one day for transient abdominal pain. Occasional substernal discomfort, not related to meals or exertion, had troubled him recently. The past history was irrelevant. There had been some dyspnea on exertion for the past two weeks. There was no ankle edema. The patient said that he was an acetylene welder who for three months previously had been working in a closed building, burning out boilers. Masks which were not very efficient had been worn to keep out the fumes, but all the workers complained of nausea and frequently vomited.

Physical examination was negative except for the following points: an icteroid tint to the sclerae, upper abdomen spastic. Later a mass was found in the left upper quadrant, believed to be spleen. Laboratory findings: the red blood count varied between 2,120,000 and 2,620,000 and the hemoglobin between 43% and 47%. The white blood count was 5,200 with 78% polymorphs. Coagulation time was 3 minutes, the clot retraction time 22 minutes, the bleeding time 90 seconds. The platelet count was 310,000. The urine was negative. The stool was negative except for occult blood. The sugar tolerance test was normal. The gastric analysis was normal except for very low free acidity. The blood fragility test was normal. An initial tentative diagnosis of bleeding peptic ulcer was made; but this diagnosis, in the light of the gastro-intestinal series, was changed to a diagnosis of bleeding esophageal varices, secondary to splenic disease, either primary splenic vein thrombosis or Banti's syndrome.

Gastro-intestinal series (14): There was a normal pattern of the mucosa of the esophagus in its upper third. The straight rugae of the proximal third blended with small oval and round snail-like protrusions (see Figs. 2, 3) encroaching upon the lumen of the remainder of the



Fig. 3. Esophogram. Same case.

esophagus. These protrusions were more pronounced on the anterior aspect of the wall and apparently rested on broad bases. The lumen of the esophagus was consequently widened in this area. An oblong shadow of the mediastinum compared favorably with widening of the mediastinum and there was a typical dilatation of the azygos vein not encountered in any other condition, as described by Grilli (15).

Course: The patient was given several small transfusions and had no gastro-intestinal complaints. However, within two weeks of admission he began to complain bitterly of constant dull pain extending from the left costovertebral angle to the umbilicus in front. The spleen was definitely enlarged to about six centimeters below the costal margin but after the subcutaneous injection of five minims of adrenalin it shrank, until within fifteen minutes, it was only just palpable. There was a questionable small amount of ascites. A diagnosis of Banti's disease was made finally and the patient was transferred to the surgical ward. Splenectomy was performed by Dr. Henry Louria six weeks after admission to the hospital. The spleen was six times normal size and firmly adherent to the under surface of the diaphragm. It was quite firm, pale in color, with a granular surface. The vessels of the pedicle were enlarged and tortuous but there was no evidence of thrombosis. The liver was half normal size, the surface pale and irregular, characteristic of the hobnail type of cirrhosis. The patient did well until two days after the operation when he became drowsy and his temperature rose to 102 degrees. The blood urea was 90 and the blood sugar 120. On the following day the patient lapsed into coma and had several generalized convulsions. There was a bilateral Babinski. The patient expired on the evening of the third postoperative day. A post-mortem examination, limited to

the abdomen, was performed and showed congestion of the pancreas, adrenal, and kidneys. The ureters and urinary bladder were normal. The gall bladder was contracted and its coat thickened. The liver has already been described. The gastro-intestinal tract was negative except for ruptured esophageal varices, the rupture being 4 cm. above the cardia. The pathological histological findings, to be reported elsewhere in detail, were those of portal cirrhosis with congestive splenomegaly.

CONCLUSIONS

1. The value of esophagrams in the demonstration

of esophageal varices, and therefore in the early diagnosis of portal hypertension, is emphasized.

2. Early diagnosis is essential if surgical intervention is to be successful.

3. A case of fatal hematemesis from ruptured esophageal varices secondary to portal cirrhosis is reported with operative and autopsy findings.

Our thanks are due to the X-ray staff under the direction of Dr. R. A. Rendich and to Dr. Ehrenpreis for preparation of the films and help in interpretation.

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The Gastro Pump

By

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THE following is a description of a simple apparatus first devised to facilitate gastric extraction and lavage in the Gastro-intestinal Clinic of the Greenpoint Hospital. The members of the clinic call it the "Gastro-Pump."

Besides gastric lavage we have found this apparatus useful for duodenal intubation, for Lyons-Meltzer drainage, for withdrawal of ascitic fluid in abdominal paracentesis, for irrigation of the urinary bladder, chest or other organs.

Description of apparatus: The "Gastro-Pump" consists of two graduate quart bottles with rubber stoppers, each having two openings. Bottle A (see diagram) has a glass tube no. (2) connected with a valve bulb no. (1). Pressure on bulb no. (1) forces air into the bottle, forcing fluid out of the bottle into glass tube no. (3). There are two stopcocks, nos. (4 and 6) connected to a Y tube no. (5). A Levine tube is inserted into the stomach and connected with the Y tube. When stopcock no. (6) is closed and stopcock no. (4) is open, pressure on bulb no. (1) will force fluid into the stomach. When the stomach is filled with sufficient fluid, stopcock no. (4) is closed and stopcock no. (6) is opened. Pressure now on bulb no. (9) will create a vacuum in bottle B and the stomach will be rapidly emptied.

Technique for gastric extraction: At 5 p. m. the day before, the patient is advised to eat a few raisins. At 9 a. m. the patient is permitted to eat a light breakfast including a roll with poppy seeds. He is instructed not to eat after 9 a. m., but may drink water. At 2 p. m. he is given 90 ccs. of 7% alcohol and twenty

minutes later the Levine tube is inserted into the stomach and connected with Y tube no. (5). Stopcock no. (4) is closed and stopcock no. (6) is opened. Pressure on bulb no. (9) causes a vacuum in bottle B which quickly empties the stomach contents into bottle B. The quantity is immediately noted by the graduation markings on bottle B. An amount greater than 90 ccs. indicates either gastric retention or hypersecretion. If poppy seeds are seen in the bottle there is six hour retention, and the presence of raisins indicates twenty-four hour retention. The contents of bottle B may then be removed for further analysis.

Technique for gastric lavage: Bottle A is filled with

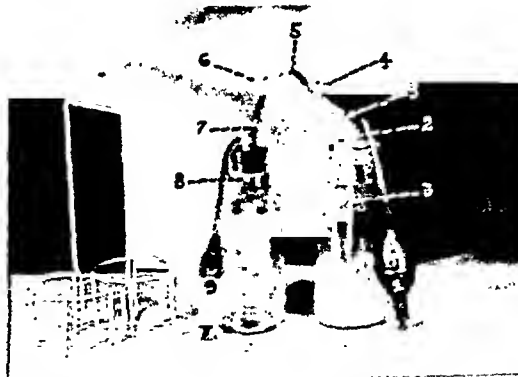


Fig. 1



Fig. 2

warm water. After the Levine tube has been inserted into the stomach, stopcock no. (4) is opened and stopcock no. (6) is closed. Pressure on bulb no. (1) forces the water into the stomach as slowly or rapidly as desired. When sufficient water has been forced into the stomach, stopcock no. (4) is closed and stopcock no. (6) is opened. Pressure on bulb no. (9) draws the stomach contents into bottle B. Bottle A may then be filled with solution of sodium bicarb or other medication desired and the procedure repeated until contents withdrawn into bottle B are perfectly clear.

Technique for Lyons-Meltzer Duodenal intubation: A Rehfuß or Einhorn tube or Twiss or Weiss tube or whatever tube is preferred, is passed into the stomach and connected with Y tube no. (5). The patient is placed on his right side. Bottle A is filled with cold water. At intervals of about five to ten minutes by opening stopcock no. (4) and closing stopcock no. (6),

about two ounces of cold water are forced into the stomach. This increases peristalsis and facilitates the passage of the bucket into the duodenum. When water is not being forced into the stomach, stopcock no. (4) is closed and stopcock no. (6) is opened, allowing drainage into bottle B. With a little experience one may recognize the different appearance of duodenal contents from stomach contents. When duodenal contents appear in bottle A, the water is emptied out of bottle A and 100 ccs. of 25% magnesium sulphate is placed into bottle A. This is forced into the duodenum about one ounce at a time to avoid nausea. If there is a question about whether the bucket is in the duodenum and fluoroscopic investigation is not possible to determine position of bucket, a few drops of Toepfer's solution may be placed in bottle B. If stomach contents are being drained the free hydrochloric acid will turn the Toepfer's solution red. Duodenal contents will change the red color to yellow.

Fractions A, B, and C usually can be seen in different layers in bottle B and finally when the clear oil like liver bile begins to appear, it can be easily seen coming through the glass tube into bottle B.

Technique for abdominal paracentesis: After having the patient urinate, a trocar is inserted into the abdominal cavity at the point desired. The trocar is connected with a rubber tube to Y tube no. (5). Stopcock no. (6) is opened and pressure on bulb no. (9) draws the abdominal fluid into bottle B. By closing stopcock no. (6) partially the rate of flow of ascitic fluid may be controlled and sudden splanchnic dilation avoided.

Technique for irrigation of urinary bladder, chest cavity or other organs: Insert Catheter into urinary bladder and connect with Y tube no. (5). Draw out urine as with gastric lavage. Inject boric acid or other solution through bottle A. Alternate injection with withdrawal.

Clinical Course of Chronic Ulcerative Colitis

(Based on 7662 Proctoscopy Examinations)

By

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INTRODUCTION

ULCERATIVE colitis remains a difficult disease to manage, difficult to get patient well and to prevent relapses. I have been engaged in the study of these cases and was interested in following them over a period of time with the hope that some plan of treatment could be found for improving the percentages of cures.

Yeomans, Bassler and Lynch (1, 2, 3) consider the disease to be of infectious origin; Thorlakson (4), Hurst (5) and Einhorn (6) refer to this entity as being primarily due to bacillus of dysentery. In 1924, Logan, Buie and Borgen (7, 8, 9) stated that ulcerative colitis was of bacterial origin and Borgen (1924) further reported the diplostreptococcus to be the specific etiologic factor. In 1926, Streicher and Kaplan (10) made clinical and experimental studies on ulcera-

tive colitis and reported that all bacteria present in the colon during the course of this disease were responsible causative factors (J. A. M. A., 1930).

It is quite obvious that in the presence of severe infection with loss in weight, diarrhea, cramping in the abdomen and loss of body fluids the individual's nutritional reserves are rapidly depleted and remain subnormal. Indeed, the nutritional factors favoring wound healing may be entirely absent.

METHOD OF STUDY

During the past eleven years we have observed 570 cases of chronic ulcerative colitis. This group may be classified as:

- Those observed once during initial proctoscopic examination
- Those treated and classified as "improved"
- Those treated and classified as "cured"
- Those treated without improvement
- Those who were unimproved and died.

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TABLE I
Data showing number of patients studied and years of "follow up"

Type of Patients	Years of "Follow Up"								Average of Group
	*1	2	3	4	*5	6	7	8	
Improved	21	18	19	19	17	8	16	23	141
Cured	0	0	3	2	6	3	5	6	25
Unimproved	15	10	7	4	2	3	2	2	45
Died	0	2	0	2	1	0	0	1	6
Total Average	36	30	29	27	26	14	23	32	217*

*Explanatory Note: In the improved group 21 cases were studied for one year and 17 cases were studied for five years; in the unimproved group 15 cases were studied for one year and two cases were followed for five years. Discussion of the groups will follow later.

Of the entire group 217 patients were observed a year or longer. These cases were observed regularly once a week or once in two weeks for a period varying from one to eight years. A standard diet was prescribed, and in addition to some medications given during the onset of the course of the disease, polyvalent vaccine was injected at weekly intervals. At the termination of each year the patient was reprotoctoscoped and observed for any changes or complications. Stool examinations were made on numerous occasions to rule out amebic infestations and to correlate the proctoscopic findings. In many instances bacteriologic studies were made of the material removed through the proctoscope during subsequent reexaminations.

CLINICAL COURSE

Unlike other gastro-intestinal lesions, the physician cannot always rely on the symptoms of this disease as an accurate index of the healing of the ulcerations in the colon. While it is probably true that the curtailment of diarrhea, the decrease of the amount of blood and pus in the stool, and the alleviation of pain in the abdomen are very helpful in determining the progress of the patient, the real criterion certainly lies in the pathologic view of the mucosa of the colon through the proctoscope. While reexamination is the method of choice one must not lose sight of the fact that at times proctoscopic examinations repeated too often, are responsible for recurrent attacks of diarrhea. These attacks run the clinical course of a "remission attack."

Exacerbations occur during acute respiratory infections or during reactivation of focal infection, but recurrences ensue less often, at longer intervals and are less severe after the patient has been on proper management. At present the general impression is that the longer the patient with ulcerative colitis remains on controlled management plus vaccination, the greater the interval of absence of recurrence after treatment is discontinued.

In Table I we are showing the number of cases observed in each group during each year.

In the course of our studies various changes were noted in these patients on proctoscopic reexamination; during these reexaminations bacteriologic cultures were made to correlate the proctoscopic findings in the colon. Whenever possible post-mortems were obtained

of the patients who have died and the findings are recorded.

In Table II we are showing the various changes noted during a period of eight years. The changes noted are again classified by groups.

In the course of our studies we have observed that about 80% of the patients are either improved or cured in due time depending on the clinical course of the case. Less than 3% meet with a mortality. The remaining 17% are unimproved or meet with a com-

TABLE II
Data showing "follow up" studies by proctoscopic, bacteriologic and post-mortem findings

Type of Patients	Proctoscopic Findings	Bacteriologic Findings	Post Mortem Changes
Improved	Fewer ulcers are seen; they are not deep, healing evident. Less edema of colon.	Fewer B. Coli per field — and fewer. Diplostreptococci Staphylococci still present. Hemolytic strept. absent. B. acidilactici present.	
Cured	No ulcerations. No edema. Evidence of healed ulcers.	B. Coli — Strept. (Viridans) ratio approaches normal limits. Hemolytic strept. absent. B. acidilactici absent.	
Unimproved	Ulcers numerous, extensive, deep. Miliary abscesses noted. Edema extensive. Marked scarring and fibrosis. Lumen narrow.	B. Coli count exagg. Strept. Viridans count increased. Staphyl. present always. Hemolytic Strept. present often.	
Died			Gross The ulcers in colon $\frac{1}{4}$ to $\frac{3}{4}$ inches wide and 3 mm. deep. Ulcers penetrate to serosa. Mesenteric glands swollen & soft. Micro: Mucosa replaced by granulation tissue, no giant cells, no ameba, necrosis of muscle layer evident.

plication which terminates fatally. It is therefore that we now wish to refer to a discussion on the complications met with during the clinical course of chronic ulcerative colitis.

COMPLICATIONS

The most common complications that we have observed in the colon are polyposis, stenosis, perforation, malignancy, and perirectal abscess. There are many other interesting and serious complications that may occur in ulcerative colitis, but they are not in the colon per se—such as endocarditis, dermatitis, nephritis, arthritis, renal abscess, cystitis and osteomyelitis. In Table III we show the complications noted and the percentage of occurrence.

TABLE III

Data showing type of complications observed and percentage of occurrence in 217 cases

Name of Complication	Number of Cases	Per Cent	Remarks
Polyposis	21	9.7	Observed mostly in Recto-Sigmoid.
Stenosis	16	7.4	In various segments of colon.
Perforation	3	1.2	Two in sigmoid, one in cecum.
Malignancy	3	1.2	Usually very malignant.
Perirectal abscess	1	.4	Uncommon.

Polyposis the most common complication is of interest because it is recognized when the patient is definitely improved (Rankin, Borgen and Buie, W. B. Saunders Co., 1935). The percentage of polyposis of the colon in chronic ulcerative colitis is about 10.5% while the percentage of polyposis without ulcerative colitis is 4%. It is important to remember that a polyp of the colon may become malignant (Mayo and Wakefield) 1936, J. A. M. A. The malignant disease is usually of the rapid, early fatal type and frequently occurring in the form of multiple carcinomas of a high grade of malignancy (Broders, 1935).

No where do we depend so much upon barium enema (roentgenoscopy) for diagnosis as we do in stenosis following ulcerative colitis because we cannot observe stenosis situated above 30 cm. with the sigmoidoscope.

PLAN OF MANAGEMENT

In the main the management resolves itself into the treatment of:

a. A group of patients of chronic ulcerative colitis who are able to eat a well balanced, basal plus diet, of low residue, high vitamin and high calory. When the acute onset of the disease subsides these patients are advised to gradually rid themselves of possible foci of infections and they are given vaccines to protect them

selves against recurrences of acute attacks. Attention along symptomatic lines is given.

b. There is another group of patients with ulcerative colitis who exhibit definite nutritional disturbances. These represent cases with a low plasma proteins, a low serum calcium, a low total base, and possibly an inverted albumin-globulin ratio. In the management of these types it is of course essential to supply fluids, liver extract, blood transfusions and other supportive measures such as Vitamin C to control hemorrhage from the colon. Later when the patient is recovered sufficiently so that healing may ensue, further treatment may be instituted.

c. Still another group is one of impending complications comprising a very small percentage. It is in this group only that surgical interference may be indicated.

DISCUSSION

It is most unfortunate that one cannot follow-up all cases observed. In general the average ambulatory ease of chronic ulcerative colitis improves on systematic management within six months or a year.

The so-called cured case usually represents prolonged care plus a very cooperative patient. The proctoscopic view of the colons of these patients is amazingly normal.

The patients that have caused us much concern are the unimproved cases. These gradually become worse regardless of the method of approach. One hesitates to remove foci of infections in these patients too rapidly because with each focal elimination there has always occurred a severe recurrent attack. As a basis for this lack of progress in these types is the presence of a hemolytic streptococcus in the cultures from the colons of these patients.

So much has been written on the surgical management of chronic ulcerative colitis that it seems desirable to mention it here briefly. Rankin said that when medical measures have failed in any advanced case, the ease will not lend itself to operation, and if some drainage operation (ileostomy) is undertaken it is with very high risk. Of the seventy ileostomy operations performed, 41 died, 10 showed good results, 2 showed fair results and 17 showed very poor results. In our series of 217 cases surgical interference has been required in three instances.

CONCLUSION

In following these cases we have learned:

1. That bed rest, dietary regime, vaccines and blood transfusions is the management of choice in chronic ulcerative colitis.
2. That proctoscopic reexaminations once yearly aids in the management of these patients.
3. That removal of foci of infections is beneficial.
4. That surgical interference should be reserved only for acute complications.

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Factors Which Reduce Gastric Acidity

A Survey of the Problem*

By

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INTRODUCTION

IT is the purpose of this review to discuss the numerous factors which may be responsible for the normal variations in gastric acidity, observed both in clinical practice and in the experimental laboratory. This problem is important because it involves several fundamental physiological processes which still await clarification; and which, once we understand them, may bring to our attention significant differences in the acidity curves associated with various clinical conditions. Furthermore, a physiological method whereby the acidity curve may be lowered significantly, as a therapeutic measure in cases of gastro-duodenal ulceration, is today one of the most pressing clinical problems in the field of gastro-enterology; and it may be that a thorough comprehension of the various factors which normally effect a reduction in gastric acidity will enable us to use one of them for the complete elimination of free acid from the stomach contents by a simple physiological procedure. Above all, however, we are concerned with a critical analysis of the basic physiological principles involved, since their practical application can come only after we have established the scientific foundation on which they rest.

Let us first of all consider the factual manifestations of acidity reduction in the stomach. At the present time, it is widely accepted that the hydrochloric acid secretion is poured into the gastric cavity by the parietal cells, ordinarily at a uniform concentration level of 160-170 mN¹ (Hollander, 1934,a). Examination of ordinary fractional test-meal curves, however, reveals the fact that the curve starts at a very low level after ingestion of the test-meal and then rises considerably, but it rarely goes above 100mN, and practically never attains a value of 150mN. The curve may then remain at the maximum for some time—the duration will vary with the individual subject—after which it will fall off again in a more or less characteristic way. In dogs provided with fundus pouches, the results are ordinarily very similar to the above, as they are also with histamine in both dog and human. Thus, at no time does the acidity in the stomach attain a value at all near that which characterizes the pure parietal secretion. Why is this so? What are the various factors which may be responsible in varying degree for this lowering of the acidity from its normal physiological maximum? Some of these

factors are obvious and unquestionable; most of them, however, are still in the hypothetical stage. The intimate mechanisms which they involve are diverse; variation in the amount of HCl actually poured into the stomach², reduction in acidity by neutralization and dilution—both of these appear to be effective in part. Moreover, some of them may be classified as extra-gastric in origin, whereas others are distinctly intra-gastric. Among the former there are:

- (1) dilution by the test-meal itself,
- (2) both dilution and neutralization by saliva, and
- (3) dilution and neutralization by regurgitated duodenal fluid.

The intra-gastric factors include:

- (4) possible variations in the composition of the parietal secretion itself (variations in the volume-rate of secretion of this fluid will not be considered here),
- (5) reabsorption of HCl, already secreted, by the gastric mucosa,
- (6) dilution by the peptic secretion,
- (7) dilution and neutralization by a distinct dilution secretion, and finally
- (8) the dilution and neutralization effects of mucus secretion from the surface epithelium.

In this review I shall attempt merely to define these several factors and to evaluate them in the light of our present knowledge. Also, I shall point out, wherever possible, what further work must be done in order to clarify present uncertainties, and to extend the information already available. In subsequent reports on this subject, we plan to adduce such additional experimental evidence, and particularly to evaluate the relative importances of these several factors in the composite picture of acidity regulation. Let us now proceed to discuss each of these factors in turn.

DILUTION BY THE TEST-MEAL

Let us consider a Rehfuß series with gruel as the gastric stimulant, wherein the fractional samples withdrawn at quarter hour intervals may continue to give gross evidence of the presence of the test meal for 2 hours or more. Each of these specimens consists in part of mixed gastric secretion and in part of test-meal—the proportions being highly variable and dependent on all sorts of chance conditions. Hence it is apparent that the acidity values as measured by direct titration do not represent the acidity of the gastric juice itself, and the shape of the acidity curve obtained in the usual way is dependent, not only on the secretory characteristics of the individual, but upon the rate of elimination of the test-meal from the stomach—that is, the rapidity and regularity of gastric evacuation. Thus, if we desire to evaluate the gastric acidity,

2. This aspect of the problem (i.e., variation in the rate of secretion of the parietal fluid) is not included in this paper. For an excellent analysis of this factor, see *Wieland, Finegan and Hill (1937)*.

1. Acid concentration in terms of milli-equivalents per liter or milli-normal (mN) is numerically equal to the number of clinical units or degrees of acidity; that is, cc. of 0.1N alkali required to neutralize 100 cc. of gastric juice. In terms of pH, an acidity value of 165 mN corresponds to a pH value of 0.57; in terms of per cent of HCl it is 0.60%.

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uncomplicated by this test-meal dilution factor, it is necessary only that we know the relative amounts of test-meal and digestive fluid present in each specimen. If we divide the observed acidity by the fractional amount of gastric secretion (or, what is the same thing, by one minus the fractional amount of test-meal) the quotient is the acidity corrected for test-meal dilution.

In order to determine the percentage of test-meal present, we must mix with the test-meal a dilution indicator, that is, some substance which lends itself readily to simple and accurate analytical determination in addition to possessing a number of other well defined characteristics. Chief among the substances used in this way are phenolphthalein (Lanz, 1921; Bloomfield and Keefer, 1927) and phenol red (Gorham, 1923; Bulger *et al*, 1928; Wilhelmj *et al*, 1933). Of these investigators, only Bloomfield and Keefer, and Wilhelmj and his coworkers, have employed the dilution indicator specifically for the purpose of correcting the gastric secretory curve for dilution by the test-meal, the former in humans and the latter in dogs. In order to illustrate the changes in magnitude and shape of the acidity curves which may be effected by instituting such a correction for test-meal dilution, let us consider one of the experiments cited by Bloomfield and Keefer, in which 7% alcohol was used as the test-meal and 10 mgm.-% of phenolphthalein as the dilution indicator (Fig. 1). As is evident from the solid line

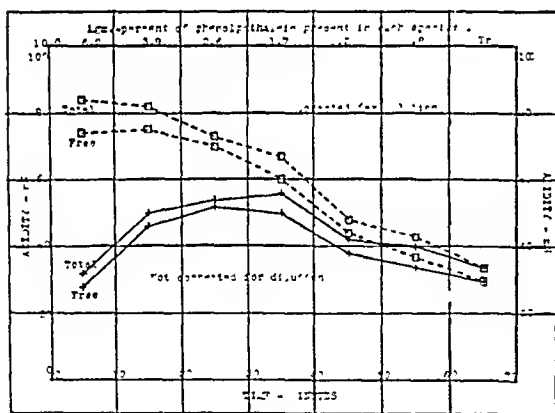


FIGURE 1

Fig. 1. Gastric acidity curves (human) with and without correction for dilution by the test-meal (50 ml. of 7% alcohol with 10 mgm.-% of phenolphthalein as dilution indicator). Data from: Bloomfield and Keefer. Arch. Int. Med., 37:831, 1926.

curves, both free and total acidities start about 30mN, rise to maxima about 55, and then fall off to the initial values or lower. The concentration of phenolphthalein present in each specimen is recorded at the top of the chart; if we divide each observed acidity by 10-this value respectively, the resulting quotations

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yield the acidity values as they would be in the absence of the test-meal dilution factor. The curves corresponding to these corrected acidities are given by the broken lines in the figure. It is interesting to note, in this particular case, not only that the first four or five

points are elevated considerably by this correction, but that the entire shape of the curve has undergone a transformation.

Unfortunately, although the principle illustrated by this comparison of uncorrected and corrected acidity curves is sound, we are not able to attach any quantitative significance to these particular observations, because phenolphthalein is inadequate as a dilution indicator. In a recent investigation of this matter (Hollander, Penner and Saltzman, 1937,a) we found that the solubility of the indicator in 7% alcohol, and therefore also in dilute acid solutions, is considerably less than 1 mgm.-%, which is its initial concentration in the test-meal employed by Bloomfield and Keefer. Consequently, a considerable amount of the phenolphthalein is slowly precipitated within the gastric cavity, which completely invalidates the calculations based on its concentration in any one specimen. Similar difficulties obtain with other substances which have been proposed as dilution indicators, with the sole exception of phenol red. At the present time we are investigating the reliability of the latter for this purpose, having already developed a simple method for its quantitative determination which is good to one per cent or better (Hollander, Penner, and Saltzman; 1937,b). Once we are assured of its dependability for these purposes, we shall be in possession of a technique for eliminating completely the influence of test-meal dilution from our studies of the more specifically physiological factors in acidity reduction.

ADMIXTURE OF SALIVA

The influence of salivary admixture with gastric contents was recognized in the earliest practices of gastric intubation. The nature of this influence is two-fold: For one thing, it reduces the gastric acidity by means of a simple dilution effect, the magnitude of which may be considerable. For another, it is generally recognized that the saliva possesses a considerable degree of titratable alkalinity, as may be illustrated by the observations of De Beer and Wilson (1932). These investigators reported a bicarbonate concentration of 55mN and a chloride concentration of 82mN (averages) for the parotid saliva of dogs under pilocarpine stimulation. Similar values have been reported for human salivary secretion. Admixture of such an alkaline fluid with the acid gastric contents must effect a considerable reduction in acidity just by neutralization alone. Likewise, the chloride concentration of the parietal secretion will undergo diminution, but this is solely a consequence of the dilution effect.

Since the rate of salivary secretion and its composition are both highly variable, it is easier to prevent admixture of saliva with the stomach contents than to devise an arithmetical correction, such as was described above for dilution by the test-meal. In fact, in clinical practice at the present time, it is usual to ask the patient not to swallow any saliva, once the tube has been passed, but to expectorate it throughout the analysis. For purposes of quantitative investigation, such a procedure is unreliable because there is bound to be some drainage into the stomach in spite of the patient's cooperation, and without this cooperation the drainage may be considerable. As for a more reliable technique for use with human subjects over a period of several hours, none such is at present available. For these reasons, it is impossible to attempt any quanti-

tative evaluation of the effect of salivary admixture on gastric acidity until such time as a suitable procedure may be devised for the purpose. In view of this, we are attempting at the present time to develop a technique for completely eliminating this undesirable contaminant from all such physiological investigations on humans, and we shall report on it as soon as progress of the work warrants.

REGURGITATED DUODENAL CONTENTS

Of all the mechanisms which have been suggested to explain the ordinary reductions in gastric acidity, the one proposed by Boldyreff (1915) has been more widely acclaimed than any other. This hypothesis states that whenever the acidity of the stomach contents is greater than about 0.15% (40mN), on passing into the duodenum this gastric fluid stimulates the flow of the several intestinal secretions and also induces a regurgitation of the duodenal contents into the stomach. Since the admixture of pancreatic secretion, bile, and succus entericus contains a considerable concentration of buffer salts, especially bicarbonate and some phosphate, such regurgitation must result in a marked reduction in acidity of the gastric contents—particularly that portion of gastric fluid which happens to be present in the antral region at the time of regurgitation. When the stomach contents, thus partially neutralized, passes into the duodenum, it no longer evokes a reflux of intestinal fluid and regurgitation is consequently interrupted until a fresh portion of more highly acid stomach contents is again passed through the pylorus—whereupon the entire process repeats itself. In short, we are confronted with an automatic process of acidity regulation, based on the inability of the duodenum to tolerate a fluid that is more acid than 0.1-0.15% HCl.

This theory has been supported by many outstanding investigators—among them Spencer, *et al* (1915); Bolton and Goodhart (1922); Hicks and Vischer (1915); Elman *et al* (1934); and more recently Wilhelmj, Neigus and Hill (1934)—although their evidence is far from conclusive. With an increase in our knowledge of the acid-base composition of the several intestinal secretions, the major responsibility for this neutralizing action came to be placed on the pancreatic secretion as over against the bile, because of the considerably higher bicarbonate concentration in the former than in the latter. Thus, Gamble and McIver (1928,b) reported the bicarbonate concentration of dogs' pancreatic juice as 79mM (the phosphate concentration was 1mM), whereas in hepatic bile from the same animal, the bicarbonate concentration was 34mM (Reinhold and Wilson, 1934). Even in human gall bladder bile the value is low; Reinhold, Ferguson and Hunsberger (1937) give a mean value of 19mM for 13 individuals without obvious bladder pathology. Of course, it may be questioned whether bicarbonate alone is responsible for this neutralizing action; perhaps the protein or other buffer salts may also play a role here, in which case the bile may be no less important than the pancreatic secretion. Further discussion of this point must be left for another occasion, but certainly the question of relative neutralizing efficiencies of the several duodenal secretions should be investigated more meticulously in terms of buffer capacity measurements.

On the other hand, it has been pointed out by Shay, Katz and Schloss (1932) that most of the support for

this theory about duodenal regurgitation is a matter of opinion rather than of observation. Thus, we find an equally imposing list of investigators (e.g., Baird, Campbell and Hearn, 1924; Yesko, 1928; McCann, 1929) aligned in opposition to Boldyreff's idea concerning the regulation of acidity within the stomach. Most of this contrary evidence, however, is based on results obtained following surgical manipulation of the stomach and duodenum. Shay and his coworkers, on the contrary, have employed a straightforward physiological technique, in humans, based on the excretion of bromsulphalein in the bile and its quantitative determination in the several specimens of a fractional gastric analysis, in which tap water, dilute HCl, or other agent was used as a test-meal. As a consequence of their well-planned and thorough study, these authors concluded that duodenal regurgitation "can and frequently does take place," but it is neither important nor regular enough to be a major factor in normal control of gastric acidity.

Furthermore, it is a well known fact that the secretory curve of an isolated fundus pouch in a dog usually manifests the same sort of deviations from maximum (parietal) acidity that are found in fractional curves from humans. For several illustrative acidity-time curves of the former variety, see Figs. 2a and 2b of the paper of Hollander and Cowgill (1931), which were obtained both with food and with histamine as stimuli. In all cases, the curves start at a very low acidity, rise to a considerable height above this value, and then fall off again; sometimes they manifest intermediate fluctuations of considerable magnitude as well. Since such a gastric pouch is completely separated from the main course of the digestive tract, it is obvious that regurgitation of duodenal contents cannot possibly be a factor in this situation. Nevertheless, we find evidence here of all the fluctuations in acidity which we observe ordinarily in the intact stomach of dog or man. Hence we may conclude that the mixture of intestinal secretions is not the sole agent of acidity reduction within the gastric cavity—nor, perhaps, even an important one. Actual evaluation of its importance in the mélange of influences must await more extensive and quantitative investigation. Whether or not the duodenal fluids are effective agents of acidity reduction in the stomach, there can be no doubt that once the gastric fluid has entered the small intestine it does come under the influence of these buffer-containing secretions—but this situation is of no concern to us at the present time.

VARIATIONS INHERENT IN THE Parietal SECRETION ITSELF

All three of the foregoing agents of acidity reduction are extra-gastric in respect to their origins. From the preceding paragraph, however, it is apparent that acidity variations of considerable magnitude may be observed under conditions such that none of these agents can possibly play a role; i.e., in gastric pouches isolated from the digestive tract proper. Consequently, we next turn our attention to the several mechanisms of distinctly intragastric origin which may be responsible for the normal lowering in acid concentration.

The first of these is inherent in the widely known theory of Rosemann (1907) which maintains that the acidity of the parietal secretion is not constant but that it undergoes variations in magnitude parallel with the variations in rate of formation of the secretion.

This view, of course, is diametrically opposed to Pavlov's earlier belief in the matter—namely, that the secretion is poured out by its parent cells at an acidity level which is relatively invariant. Rosemann based his argument on the following: (1) Direct and universal observation of variation in acidity in the course of any single experiment with dogs, the variations being unmistakably correlated with the rate of secretion. (2) A belief that variations in acidity may occur even in the absence of mucus, the agent which Pavlov held to be chiefly responsible in this respect. (3) In general the concentration of total chloride (both acid and neutral chloride) varies but slightly, an observation which is demanded by Rosemann's hypothesis and is consistent with his entire view of the process of formation of the gastric HCl.

In the course of an extensive review of these opposing theories of Pavlov and Rosemann (Hollander, 1934), each of these specific arguments was analyzed and refuted in turn. Thus, it can be shown that the rate of secretion and the acidity in dogs are not always parallel with each other, and that the chloride concentration is not constant, but decreases as the acidity diminishes, though at a much slower rate. Also, it was possible to demonstrate by direct experimental evidence that Pavlov's contention is the correct one; i.e., that if the proper experimental conditions be maintained, acidity values may be relatively constant over a long period of time and independent of the individual animal or the type of stimulus employed (food or histamine). True, the acidity of the parietal secretion varies with changes in osmotic pressure of the general circulation—according to the views which are more recent than those of Rosemann (Gilman and Cowgill, 1933; Hollander, (1934,b)—but these osmotic changes, by their very nature, must be small compared with those which occur in the fluid of the gastric cavity. Hence, it may be concluded that at least this particular mechanism cannot be held accountable for acidity regulation either in the dog or, most likely, in the human.

ABSORPTION OF HYDROCHLORIC ACID BY THE GASTRIC MUCOSA

The notion that the concentration of HCl within the intact stomach or the stomach pouch may be reduced by a physical process of absorption is one which as yet has not acquired many adherents. Without offering any experimental evidence to support their contention, Shay, Katz and Schloss (1932) conclude that "with the introduction of acids into the stomach (of humans), some very rapid mechanism is brought into play. This mechanism, being neither one of neutralization nor of dilution, we believe is very likely one of absorption." According to this view the HCl would be taken into the gastric mucosa—presumably along with water molecules—and passed on to the tissue fluid and hence into the general circulation.

A modified version of this mechanism has been advanced by Teorell (1933). This investigator believes that, as HCl diffuses out of the stomach, through the mucosal wall, neutral chloride (e.g., NaCl) passes into the gastric cavity. More technically, there exists normally across the gastric mucosa an exchange of H-ion from the gastric juice and Na-ion from the tissue fluid or blood. Although Teorell did not demonstrate directly that such an ionic interchange occurs

in the mammalian stomach, he did perform numerous physico-chemical experiments of an analogous nature. In these experiments, solutions of HCl and NaCl were separated by non-vital membranes, and the changes in H-ion and Cl-ion concentrations which he obtained were quantitatively similar to those which were observed, for instance, on placing mixtures of HCl and NaCl in a cat's stomach in an acute experiment.

Although these views are certainly worthy of consideration and even of experimental examination, yet, so far as I know, they have received very little of either. Nevertheless, there are several considerations which throw considerable doubt on the likelihood that any such process of absorption, with or without ionic interchange, actually occurs. For one, a process of this kind can in no way account for the low acid values at the beginning of secretion, although it may explain the post maximal drop in acidity. For another, certain observations of my own, I believe, contribute evidence in disproof of both of these absorption mechanisms. This evidence is based on an extensive series of experiments on the acidity of gastric juice which has been formed in dogs' fundus pouches and kept there by means of a sphincter action on the mouth of the pouch. Under such conditions, it was found that gastric secretion could be retained in the pouch for considerable periods of time without giving any indication of having suffered a significant diminution in its acidity. Observations of this kind were made with juice of acidity values as high as 150mN, and for time intervals as great as 9 hours. Occasionally, fluid collected from such a pouch did possess an acidity considerably lower than the maximum for pure parietal secretion, but this reduction was shown to be the result of dilution and neutralization by non-acid fluid which was present within the pouch before secretion started. When this contaminant was washed out, by discarding the first portion of juice secreted, the acidity of the subsequent portions remained quite invariant, thus supplying positive evidence in refutation of acidity reduction by absorption. Of course, it might be argued that the absorption occurs through some part of the gastric mucosa other than that included in the fundus pouch. The validity of this objection cannot be questioned, though I doubt its probability; in any case, now that the hypothesis has been advanced in the gastric literature, it must be given full consideration and investigated from various aspects.

EVIDENCE FAVORING SECRETION OF A BUFFER CONTAINING FLUID

Before going on to consider the remaining factors which may play a role in acidity reduction, let us stop to examine a considerable body of evidence which, I believe, proves well-nigh conclusively that reduction in acidity is associated with the presence of substances which are not contained in the parietal secretion itself. Some of this evidence is derived from my own investigations; the bulk of it is cited from the work of others. The facts are as follows:

(1) When gastric juice from fundus pouches was analyzed (Hollander, 1934,b) for various chemical constituents—i.e., neutral chloride, combined acidity, total solids, ash, and phosphate—it was found that all of these substances are present in specimens of lower acidity and in concentrations of significant magnitude. With rise in acidity of the specimen, however, the concentration of each of these constituents diminished

(Table I) until, in the specimen of highest acidity investigated (158mN), combined acidity and total phosphorus were entirely absent, neutral chloride was down to 5mN, and total solids had dropped to 0.12%—of which organic solids comprised 0.04% and inorganic solids the remainder. These decreases were all progressive throughout the range of acidity studied. It follows, therefore, that there is a definite negative correlation between the acidity of gastric juice and its

TABLE I

Variation in concentrations of various chemical constituents of dogs' gastric juice with acidity (from Hollander, 1934,b)

Specimen Number	1	2	3	4	5
Total acidity, mN	111	135	144	155	158
Free acidity, mN	107	133	141	153	156
Combined acidity, mN	4	3	3	2	2
Neutral chloride, mN	25	22	18	7	5
Organic phosphorus, mN	—	—	—	0	0
Inorganic phosphorus, mN	—	—	—	0	0
Total solids, %	0.35	0.24	0.20	0.13	0.12
Ash as chloride, %	0.20	0.17	0.12	0.09	0.03
Organic solids, %	0.15	0.05	0.05	0.04	0.04

content of the several chemical factors enumerated, a correlation which can be explained best, if not solely, by the addition to the parietal secretion of varying proportions of a non-acid fluid which contains alkali salts, protein, phosphate, etc.

(2) Similar observations on human gastric juice have been reported by Helmer (1934), with histamine as the stimulus. This investigator studied total base (equivalent to neutral chloride), nitrogen, phosphorus, and mucous sugar, in a series of specimens of different acidities, and found that the concentrations of all four of these chemical constituents increased as the acidity diminished. Webster (1930) found the same to be true for neutral chloride and protein, the latter determined by precipitation and weighing. Likewise, Pollard, Roberts and Bloomfield (1928) observed that changes in nitrogen and total base concentrations are parallel in histamine secretion from human subjects, and that the values for both increase as the total acidity falls off. Dienst (1931) determined the total nitrogen concentration in 86 samples of human gastric juice, free of saliva and bile, and obtained results which are wholly in accord with these others.

(3) In order to determine the nature of the buffer substances which are present in gastric secretion and which manifest themselves on titration as "combined acidity," Mitchell (1931) studied the effect of titration, dialysis, and aeration on fasting contents from human stomach. He also studied pilocarpine and histamine juice from the stomachs of dogs. As one might expect, he found considerable amounts of protein and protein degradation products, with some phosphate in small amount. In non-acid secretion (i.e., fluid with an acid deficit, like the pyloric secretion) by far the greater part of the buffering power was found associated with

alkaline bicarbonates. His evidence for these statements appears to be incontrovertible.

With this array of facts before us there can be little doubt that the usual lowering of gastric acidity is quantitatively correlated with the concentrations of a number of substances which, by their very chemical natures, must be causative agents in this lowering. Furthermore, this correlation obtains, not only for the intact stomach of man and dog, but for isolated stomach pouches in the latter animal as well. Thus, our problem would seem to narrow down to a search for one or more non-acid, buffer-containing fluids which are elaborated by the gastric mucosa itself. The action of such a fluid would be two-fold: one of neutralization and the other of dilution; which of these is more important will depend on the nature and concentration of these buffer substances. Let us therefore proceed to consider the various secretions which may possibly function in this respect.

PEPSIN SECRETION

The first of these fluids to be considered is the enzyme-containing secretion of the peptic or body chief cells. About the composition of this fluid we know practically nothing at the present time except that it contains the pepsin and probably also the rennin. Nor can we say anything about its volume relative to that of the parietal secretion, nor about its content of salt or buffer substances. It seems fairly likely, however, that the volume-rate of secretion of this fluid is extremely small, even when compared with the volume of mucus secretion. This might explain why studies on the correlation of acidity and pepsin activity are manifestly inconsistent. Clinical studies like those of Hirsch-Mammoth and Rindfleisch (1925), and Butcher (1926) frequently indicate a parallelism of the acidity and pepsin curves for any one subject. On the other hand, it has been pointed out by Gilman and Cowgill (1931) that in general "the highest proteolytic power of dog's histamine juice was associated with low acidities, (and) conversely high acidities may be associated with very low pepsin." In keeping with this finding these workers observed "a parallelism between pepsin and neutral chloride concentration in the gastric juice." The best investigation of the correlation of acidity and pepsin in humans is the statistical study of Vanzant, Osterberg, Alvarez and Rivers (1933) on 85 normal persons and 274 patients with duodenal ulcer. Following an Ewald test-meal the correlation coefficients of pepsin activity and free HCl were 0.51 and 0.65 for these two groups respectively; for gastric juice obtained after histamine stimulation, the ulcer group showed a correlation coefficient of 0.60. With values so low it is altogether impossible to assert the existence of any sort of well-defined statistical correlation between the two variables, but since the coefficients are in all cases positive it is probable that the general tendency is in the direction of increasing enzyme activity with increasing acidity. So, it may be assumed that if the peptic secretion plays any part in acidity reduction, its role is an extremely minor one and may therefore be dismissed for the time being.

THE DILUTION SECRETION

Even well before the end of the last century, it was reported that, when hypertonic solutions of HCl, NaCl, or glucose are introduced into the intact stomachs of humans or dogs, or into stomach pouches of the latter,

such solutions undergo a progressive decrease in concentration. (Roth and Strauss, 1899; Smith, 1884, and Von Mering, 1893). The processes suggested to account for this decrease in concentration were threefold: (1) osmotic diffusion, (2) secretion of HCl and pepsin-containing fluids, and (3) secretion of a specific "Verdünnungs Sekretion" or dilution secretion. Particular emphasis was placed on the last of these, although no direct evidence was adduced in support of its occurrence, nor was any suggestion made as to its possible chemical composition. Subsequent workers went so far as to suggest that this unknown secretion might be a solution of neutral chloride, with or without some source of alkalinity or buffer substance (see, for instance, Liu, Yuan and Lim, 1934; also Engstrom, 1935); various other names, such as "Nebensekret" and "accessory" secretion were proposed for this fluid.

Actual evidence regarding its chemical make-up was not forthcoming until the present decade, when Webster and Komarov (1932) reported that gastric juice from various sources contains soluble muco-protein, which is distinct from the mucus of the surface epithelium and which, they believed, is secreted directly by one of the gastric gland cells. In the same year, I pointed out (Hollander, 1932) that the quantitative relation which exists between the concentrations of neutral chloride and of acid in dogs' fundus pouch juice could be explained very satisfactorily by the presence of an "alkaline constituent" of the gastric juice, the acid-base composition of which is similar to that of blood plasma; i.e., an isotonic solution of alkali and alkaline earth chloride, bicarbonate, phosphate and proteinate, with the neutral chloride concentration in the neighborhood of 100mN. This "alkaline constituent" might conceivably be a mixture of mucus, peptic secretion, epithelial detritus and possibly a secretion corresponding to the "dilution secretion" of Roth and Strauss. This hypothesis was subsequently supported by some evidence of Wilhelmj and his coworkers on the neutral chloride concentration of the non-acid secretions of the stomach (Wilhelmj, Neigus and Hill, 1934; Wilhelmj, Henrich and Hill, 1934). However, these investigators believe that the non-acid constituents of the gastric juice play only a secondary role in acidity regulation, and that duodenal regurgitation is of far greater consequence in this process.

Viewed from its histological aspect, also, the concept of a specific "dilution secretion" is entirely tenable. In addition to the mucous cells of the surface epithelium there are three other kinds of cells in the gastric tubules: the peptic cells, the parietal cells and the mucoid cells (also called the neck chief cells, Zwischenzellen and Nebenzellen). The function of the latter is quite unknown, but Babkin (1931) has suggested that they may be the source of the soluble muco-protein of gastric juice and hence of this dilution secretion.

It appears, from the foregoing, that there is already considerable evidence in favor of the existence of a specific non-acid gastric secretion which plays a role in acidity regulation. It is essential now that direct experimental efforts be made to establish the existence of such a fluid and to determine its various chemical characteristics.

THE MUCOUS SECRETION

We have already considered two possible sources of buffer-containing secretion from the gastric mucosa.

The third (and remaining) possibility is mucus, the viscous secretion which is elaborated by the surface epithelium. It has long and universally been recognized that, thanks to its high viscosity and adhesiveness, this fluid exercises a protective function against mechanical abrasions of the inner gastric wall. That it may also act chemically to neutralize the HCl is an idea that can be traced back to the early days in Pavlov's laboratory (Pavlov, 1910). These workers made no attempt to elucidate the chemical processes involved, but they undoubtedly credited the mucus with a major part of the acid-neutralization which occurs within the stomach. This view has found many champions during the intervening years, but it has also encountered considerable resistance. Much of this opposition has come from Rosemann and his supporters, the views of whom we have already discussed. Before analyzing the arguments which have been advanced against the acid-neutralizing role of mucus, let us consider what is known today about the chemical properties of this secretion.

In the first place, we must differentiate between *mucus* and *mucin*. The latter is a solid, a distinct chemical substance of the class of conjugated proteins, and it forms one of the constituents of the mucous secretion proper. The native secretion from the surface epithelium, on the other hand, is a homogeneous fluid, highly viscous, tenacious, transparent (its frequent opalescence is probably due to epithelial detritus) and odorless. Different investigators have collected it from whole stomachs, fundus pouches, or pyloric pouches. The assumption that the secretion from the pyloric antrum is practically identical with the HCl-free fluid from the fundus is generally accepted at the present time, although it is recognized that the relative amount of pepsin secretion which is mixed with the mucus may differ in the products obtained from the several sources.

Let us next compare the essential chemical properties of the gastric mucus as reported by these various investigators. As is evident from Table II, some of the earlier workers observed that its reaction to litmus was neutral or even distinctly acid—which corresponds to a pH value of no greater than 7.0 and possibly even less than 6.0. However, as early as 1901, Schemiakine (in Pavlov's laboratory) found that the pyloric secretion from the dog may be distinctly alkaline. Subsequently, it was pointed out that an alkaline reaction to litmus is far more common than an acid one; in fact, a pH appreciably greater than 7.0 may be obtained consistently if the following precautions be taken: (1) In the preparation of the pyloric pouches, it is essential that the fundus mucosa (i.e., that containing the parietal cells) be completely excluded; and (2) in the collection of mucus from fundic pouches, it is essential that the acid-forming cells be in the resting state, even if it be necessary to inject atropine for their inactivation. Thus, it is not surprising that Gamble and McIver (1928,a) were able to attain a pH value as high as 8.4. In some of the recent work in this laboratory we have reached values above 9.0—as indicated by a distinct pink coloration to phenolphthalein. Although we have observed this high value repeatedly, the conditions essential for obtaining such a markedly alkaline fluid have not yet been worked out

3. It is important to remember that a solution may be distinctly acid to litmus and yet possess a pH value which differs from neutrality by no more than 1 pH unit, i.e., no less than 6.0.

completely, and we are engaged at present in attempting to learn more about its source and significance.

So much for our present knowledge concerning the pH of the mucus secretion; let us now digress to consider why the pH is wholly inadequate as a measure of titratable alkalinity or acidity. Physical chemists generally admit that, of two solutions possessing different values, that having the lower pH (i.e., the more acid) may actually possess a greater neutralizing power for free HCl than the solution of higher pH value, although this is not necessarily so. One condition requisite for this anomalous situation is this—that the more acid solution possess a higher concentration, in terms of normality, than the more alkaline one. Such a difference in neutralizing power corresponds to a difference in buffer capacity, a concept which is applicable to acids and alkalies as well as to buffer salts. By way of illustrating this principle, let us compare a 0.01 N solution of NaOH with a 0.1 N solution of NH_4OH . The pH of the NaOH is 12.12,

going discussion has one very important and practical implication: since we are interested in the acid-neutralizing power of the mucous secretion, it is essential above all else that we know its titratable alkalinity. The pH value is important on other scores, but it tells us nothing about the ability of the mucus to neutralize the HCl of the parietal fluid. Reference to Table II, column 5, reveals only three references to the titratable alkalinity. Gamble and McIver (1928,a) reported a value of 11 mN for the alkalinity of the pyloric secretion of the cat, and Bolton and Goodhart (1931) found values of 30-44 mN for the non-acid fluid from the whole stomach of the same animal. For the dog, the only such data on record—so far as I have been able to find—are those of Schemiakine (1904) who reported titration values in terms of Na_2CO_3 which vary from 0.026 to 0.081% (average: 0.048%). These numbers correspond to 5-15 mN (average 10 mN) respectively. It is evident from these values that the fluids studied possess the ability to neutralize gastric acidity to some degree, and it is possible that the pure

TABLE II
Chemical properties of mucus secretion from the gastric mucosa

Investigators	Source	Litmus React.	pH	Alk'y (mN)	Tot. Base (mN)	Tot. Cl. (mN)	Tot. Solids %	Tot. Ash (%)	Pepsin	Sp. Gr.
Contjean (1923)	Dog — p.p.p.	Ac.								
Schemiakine (1904)	Dog — p.p.p.	Alk.		5-15						
Ivy and Oyama (1921)	Dog — p.p.p.	Ntr.	7.0-7.5			125-180	1.3-2.4	0.6-1.5	—	1.008-1.011
Takata (1922,a)	Dog — wh. st.	Ntr.Ac.					1.5	0.5	+	1.006-1.007
Takata (1922,b)	Dog — p.p.p.	Alk.	7.4-8.0			150		0.54*	+	1.009-1.012
Lightstone (1926)	Dog — p.p.p.	Ac.			169					
Gamble and McIver (1928,a)	Cat — p.p.p.	Alk.	8.4	11		158	2.5			
Webster (1930)	Dog, cat — wh.st.	Alk.				110-130	Variable		+	
Bolton and Goodhart (1931)	Cat — wh. st.			30-44		80-102				

Abbreviations: p.p.p.—pyloric pouch; wh.st.—whole stomach; Ac.—acid; Alk.—alkaline; Ntr.—neutral; Tot.—total.
*Average Value.

whereas for the NH_4OH it is 11.27 and therefore more acid by almost a whole pH unit; yet, volume for volume, the NH_4OH will neutralize 10 times as much HCl as will the NaOH. The anomaly becomes even more marked if we compare 0.01 N NaOH with an $\text{NH}_4\text{OH} - \text{NH}_4\text{Cl}$ buffer mixture in which the concentrations are 0.1 N and 0.8 N respectively. In this case the presence of the NH_4Cl actually decreases the pH of the NH_4OH to 8.4; this is 2.9 pH units less alkaline than the 0.01 N NaOH. Nevertheless, the ability of the $\text{NH}_4\text{OH} - \text{NH}_4\text{Cl}$ buffer mixture to neutralize HCl remains practically identical with that of the salt-free NH_4OH and 10 times that of the NaOH of considerably higher pH value¹.

To the uninitiated, this distinction between pH and titratable alkalinity or neutralizing power is undoubtedly confusing, yet it can be justified on both theoretical and empirical grounds. An explanation of the whys and wherefores of this differentiation is so technical and so involved as to be quite impossible at this time. For our present purposes, however, the fore-

mucus secretion, were we able to collect if free of all contaminants, might be found to possess an even higher value for the titratable alkalinity. In view of the scarcity of evidence on this score, it is apparent that a considerable amount of investigation of this most important property remains to be done. Such a study must be systematic and should attempt to correlate the variations in alkalinity with the concentrations of the several other constituents of the secretion.

Concerning the other chemical characteristics of mucous secretion, there is nothing that can be said with any assurance. For the total base content (i.e., the metallic ions Na, K, Ca, and Mg), only one value has so far been reported; Gamble and McIver found 169 mN in a single specimen composed of a number of separate collections. This value suggests that the mucus secretion may be isotonic with mammalian blood, just like the parietal secretion, but in order to justify this important generalization it is necessary that their finding be confirmed by independent investigation. Also it must be shown that the total base value remains practically invariant under a variety of phy-

1. The pH-concentration data for the foregoing calculations were taken from Michaelis (1926).

siological conditions, except such as likewise induce a change in the osmotic pressure of the blood itself.

In the case of the total chloride concentration, no such constancy has been reported, although 8 of the investigators have reported values for this constituent. In those investigations where at least several determinations of chloride concentration have been made, a considerable range of variation is noticeable; the greatest such variation is that observed by Ivy and Oyama (1921) who reported a range from 129 mN to 180 mN. It is noteworthy that no other investigator has reported a value as high as 180 mN, but that Bolton and Goodhart (1931) obtained values as low as 80 mN. What significance attaches to this high variability in chloride values it is impossible to say at this time. It may be that the variability is inherent in the very nature of the secretion, in which case it is important to discover what are the physiological factors which determine the chloride content of any one specimen. On the other hand, the total chloride concentration may be relatively constant, as in the case of the parietal secretion, and the observed variations may result from the admixture of other fluids like the pepsin and mucoid secretions. If this be the case a way must be found for collecting the mucus secretion more or less free of these contaminating secretions so that its properties may be studied in a state of relative purity.

For total solids and total ash (inorganic solids), the percentile values likewise show considerable variation. The highest value reported (Gamble and Melver, 1928,a) for total solids is 2.5%, which is high indeed. Since Ivy and Oyama reported a value which is practically identical it may be that this value is actually characteristic of the secretion itself, but this fact must be confirmed on a considerable series of specimens before we can accept it. Three out of four studies report the presence of pepsin; only Ivy and Oyama were able to obtain an enzyme-free product. In view of the presence of peptic cells throughout the entire fundus and in a considerable part of the pyloric antrum as well, it is not surprising that difficulty has been experienced in obtaining mucus which is pepsin-free. For a long time it was believed that the pyloric glands are pepsin-forming, a theory which can be traced back to Heidenhain, but thanks to the histological work of Bensley (see Ivy and Oyama, 1921) there is no longer any doubt concerning the error of this view. Values for specific gravity are also included in the table, but since this property is dependent on the content of total solids, it merits no further discussion at this time.

ARGUMENTS AGAINST MUCUS AS A MAJOR FACTOR IN ACIDITY REGULATION

From the foregoing discussion of the chemical characteristics of gastric mucus, it would appear that this secretion may well function as an agent of acidity reduction in the stomach. However, two specific arguments have been advanced in opposition to this possibility. These are (1) that the secretion is not sufficiently alkaline to be effective, and (2) that its volume-rate of secretion is so low as to be insignificant in the presence of any but the smallest quantities of parietal secretion. To these I should like to add a third possible objection; namely, that the chemical properties reported for mucus secretion may be due in great part to the presence of some other non-acid secretion. Let

us consider the validity of each of these objections in turn.

Concerning the question of inadequate alkalinity, we have already seen that pH values as high as 8.0-8.4 have been reported for dog and cat, though by no means consistently. Also, from our own unpublished observations, there is some reason to believe that the normal pH value in the latter animal may sometimes run as high as 9. Furthermore, I have already shown above that the "titratable alkalinity" is a far more significant criterion of neutralizing power than the pH, and titration values as high as 44 mN have actually been observed in the case of the cat. It must be admitted that no one has yet attempted a systematic investigation of the titratable alkalinity, but there can be no doubt, even at this early time, that the value is sufficiently high to permit of an appreciable degree of acid-neutralizing power.

The second objection, that concerning the inadequate volume of mucus secreted, is a more serious matter. Judging by the volume of precipitated mucin present in the average sample of gastric juice from an experimental pouch dog, the volume of mucus, relative to that of the parietal secretion, is small indeed. But, so far as I know, there is no published evidence to indicate that the volume of mucin precipitated from a sample of gastric mucus is even approximately the same as the volume of native secretion from which it was derived. Again, it has been pointed out that the volume of mucus secretion obtained from a fundus or whole stomach pouch by gentle massage of the mucosa is invariably small, and nobody has yet been able to devise a method for increasing it appreciably. Chemical irritants like AgNO_3 and mustard oil do yield a larger volume, but the fluid is in the nature of an inflammatory exudate rather than a true secretion (Bolton and Goodhart, 1931). Consequently, until we are in possession of more extensive evidence on the normal physiological stimulus to mucus flow we are forced to admit the utter inadequacy of this alkaline secretion as a major factor in the process of acidity regulation.

Likewise with the question of purity of the material which has been called mucus secretion by the various investigators who have worked with it. Sometimes the acid-free product from the gastric mucosa is as viscous as a partially dried mucilage, whereas on other occasions it behaves like a fluid of merely moderate viscosity. Does this variability in viscosity betoken merely a change in physical characteristics which results from differences in physiological conditions of formation and secretion, or does it betoken the presence of some other, highly fluid, acid-free, secretion mixed with mucus of extremely high viscosity and adhesiveness? Certainly, in the absence of specific evidence to the contrary, we must admit the possibility that much of what is being called mucus is actually a mixture of this secretion with the mucoid or dilution secretion which has already been discussed above. One might expect a fair degree of constancy in the chemical properties of so specific a secretion as mucus, and the high variability in the analyses reported is further evidence of the presence of at least two secretions from different cellular sources in this fluid which has been accepted for analytical purposes as pure mucus.

Granted the actuality of such contamination, we are then confronted with these possibilities: either (1) the neutralizing power of pure mucus secretion is even higher than that indicated by the observations of

Table II (2) or else, it is considerably lower and the bulk of the titratable alkalinity reported by Schemiakine, Gamble and Melver, and Bolton and Goodhart is contributed by the diluting secretion. For the time being, therefore, we must rest content with the knowledge that mucus from the surface epithelium may be an important factor in the process of intra-gastric acidity regulation. By the same token, however, its influence in this regard may be wholly negligible and its chief function in the gastric cavity may be that of a mucosal lubricant against mechanical and chemical irritations. And so again we are confronted with a lack of factual information which must be remedied before we can possibly formulate any precise ideas along these lines.

CONCLUSION

The foregoing discussion attempts to present all the factors in the course of a gastric analysis which co-operate in lowering the normal gastric acidity from its initial high value of the parietal secretion. One of these—admixture of test meal with stomach contents—is extraneous and non-physiological, and a method has been described whereby in future investigation its influence can be corrected for quantitatively. A second of these factors—variations in composition of the parietal secretion itself—finds little support today by reason of the evidence which has already been accumulated against it. The six remaining factors—admixture of saliva, regurgitated intestinal contents, peptic secretion, a specific dilution secretion, mucous secretion, and reabsorption of HCl—are all possibilities which require painstaking investigation. Thus, this discussion is intended to serve as an analysis of the broad problem of acidity regulation, looking forward to a quantitative evaluation of these several factors. From the evidence presented, there can be little doubt that the observed variations in gastric

acidity are due primarily to neutralization by buffer substances—protein, phosphate, and bicarbonate—and to dilution by the fluids which contain them. But which are these fluids, and is there one which serves to a greater degree than any other in the capacity of buffer-containing secretion?

From one aspect this problem reduces to the question: What are the physiological factors which give to an acidity curve the particular shape it has? To this extent it is essentially academic in interest, even though fundamental. From another aspect, however, the problem deals with the mechanism by which the body normally reduces the acidity from a value in the interval 160-170 mN to one considerably lower and which the mucosa can tolerate without detriment to itself. Considered from this angle, the problem is a vital one for the clinical gastro-enterologist who is concerned with a procedure which he can utilize to reduce or eliminate free acidity wherever this may be indicated. With a complete understanding of all the factors involved in this acidity reduction process, it is hoped that we may eventually be able to avail ourselves of at least one of them as a physiological therapeutic measure in cases of gastric or duodenal ulcer. Such a practical application requires a knowledge, not only of the chemical processes involved in the action of this factor, but also an understanding of the stimulatory mechanism whereby this factor can be evoked. Thus, even for so utilitarian a purpose, we find ourselves under the primary necessity of unraveling these fundamental physiological phenomena—which means simply that the physiology of the gastro-intestinal tract is still a very young science and that much research remains to be done before it assumes as prominent a place in our text-books of physiology as is commensurate with its importance.

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The Gastric Secretory Curve Before and After the Mann-Williamson Operation, and its Bearing on the Normal Regulation of Gastric Acidity

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IN previous publications (1, 2, 3) it was shown that there are two distinct and separate mechanisms normally responsible for the control of gastric acidity, namely *duodenal regurgitation* and *acid inhibition*. Duodenal regurgitation becomes most pronounced near the end of the gastric secretory curve and results in the entrance of non-acid duodenal secretions into the stomach. Acid inhibition becomes active when the acidity of the gastric contents reaches a certain threshold value and results in a decrease in the amount of acid secreted without a change in its concentration. The inhibiting action of the acid gastric contents is exerted by an effect in both the stomach and the intestine.

In the normal intact stomach these two mechanisms are in operation simultaneously and it is very difficult to determine the exact role played by each. In order to separate them, the gastric secretory curve was previously studied in whole stomach pouches and compared with the curve found in the intact normal stomach (1). Although the results of these studies were very definite, they were open to criticism, first because of the use of the whole stomach pouch preparation, and second because the comparisons were not based on the findings in the same animal before and after the operation. In order to meet these criticisms and to obtain further information regarding the exact role played by these two mechanisms, the problem has been reinvestigated using the Mann-Williamson operation in which the duodenal secretions are drained into the terminal ileum but in which the continuity of the gastro-intestinal tract is re-established.

METHODS

A two percent Liebig's extract test meal containing 15 mgs. of phenol red per liter was used in all studies. The methods and calculations employed have been described in previous publications (1, 4). From 7 to 10 satisfactory fractional gastric analyses were obtained on each animal before operation and, on most dogs, from 9 to 12 fractional analyses after operation. Samples were removed from the stomach every half hour for two hours or until the stomach emptied. The stomach was emptied as completely as possible when the last sample was removed. On each gastric sample the following analyses were made:—percent of phenol red, milligrams percent of total chloride and neutral chloride (and by difference the acid chloride), a Pettenkofer test, and the total titratable acid using Brom cresol purple as an indicator.

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The Mann-Williamson operation (Surgical Duodenal Drainage) was performed according to the original technique. The stomach was separated from the duodenum and the upper end of the duodenum was closed. An end to end anastomosis was made between the pyloric end of the stomach and the upper end of the jejunum. Great care was taken to avoid mechanical narrowing at the site of the anastomosis and when necessary the lumen of the jejunum was enlarged by an incision of the wall opposite the mesenteric attachment. The lower end of the duodenum was drained into the ileum by a small side to side anastomosis 6 to 8 centimeters above the ileo-caecal valve. The animals recovered promptly and studies were started on the 9th or 10th post-operative day and were usually continued until signs of ulcer appeared.

The usual kennel ration of dog biscuits, milk and karo syrup was given except on days preceeding an experiment when only milk and syrup was given.

Because of the delayed emptying time encountered after operation, the stomach was always carefully lavaged, before introducing the test meal, with three or four 300 cc. portions of the test meal to be used or until the lavage returned perfectly clear. This was done in order to remove any food or residual secretion present in the stomach.

RESULTS

Five dogs were studied both before and after operation and one dog only after operation. A total of 43 fractional analyses were performed before operation and 51 after operation.

I. The Average Secretory Curves Before and After Operation. (Figure 1 and Table I.

The average secretory curves after operation were decidedly different from those before operation. The differences involved chiefly the acid chloride concentration of the total secretions and the amount of non-acid secretion entering the stomach. Before operation the acid chloride concentration of the total secretions entering the stomach rose rapidly during the early part of the curve and usually reached its peak during the first or second half hour period; following this there was a decrease which was often very sharp and which continued until emptying of the stomach occurred. The amount of non-acid secretion entering the stomach before operation was relatively small during the first part of the curve but near the end there was an abrupt relative increase and accompanying this increase bile nearly always appeared in the gastric contents.

After operation the acid chloride concentration of the total secretions entering the stomach continued to

rise throughout the entire curve, the final drop being entirely absent, and the values reached were usually much higher than before operation. The amount of non-acid secretion entering the stomach was often nearly normal during the first and second half hour periods but instead of the normal abrupt increase before emptying occurred there was usually a decrease, so that the final samples frequently contained no non-acid secretions. Bile was absent from the gastric contents.

These striking differences in the average curves before and after operation are undoubtedly due to the fact that normally there is regurgitation of non-acid secretions from the duodenum, near the end of the curve, which by dilution and neutralization (5) lower the acidity of the *total secretions* entering the stomach. Regurgitation of duodenal secretions ordinarily does not occur after the Mann-Williamson operation.

II. Unusual Curves After Operation.

Out of a total of 51 experiments performed on five dogs after operation there were 9 in which the non-acid secretions increased near the end of the curve and in 6 this was accompanied by a decrease in the acid

chloride concentration of the secretions. These curves rather closely resembled the normal curves before operation. Five typical examples are shown in Table II. It appears quite certain that the non-acid secretion which entered the stomach in these experiments was intestinal contents which was forced from the jejunum into the stomach. The evidence for this statement rests upon the following facts: 1. In two such experiments fecal masses were found in the stomach before starting the experiment and in the gastric samples removed during the experiment. In a third experiment the gastric samples had a distinctly fecal odor. Except in these instances the gastric contents were very clean and practically odorless. 2. In two experiments the last gastric samples removed gave faint but unmistakably positive Pettenkofer reactions, thus indicating that some of the regurgitated intestinal material had come from the lower ileum. Matthews and Dragstedt (6) have shown that when the duodenum is anastomosed to the ileum as high as 40 cm. below the gastro-jejunoostomy there is often regurgitation of sufficient amounts of duodenal secretions into the jejunum to protect it from ulcer. This fact was also observed by Mann (7). It is therefore not

TABLE I

Per Cent Phenol Red	cc. N/10 HCl secreted per 100 cc. gastric contents	Total Secretions cc.	Acid Secretion cc.	Non-acid secretion cc.	cc. N/10 HCl per 100 cc. of gastric secretion	Bile	Time Hours	Volume of gastric sample cc.	Remarks
91	11	9	6	3	122	0	½	35	Average of 7 experiments before operation
71	37	29	22	7	128	++	1	37	
38	51	52	36	26	99	+++	1½	38	
33	58	67	34	33	87	+++	2	33	
96	6	4	4	0	150	0	½	39	
93	11	7	6	1	167	0	1	37	
89	15	11	9	2	136	0	1½	35	
62	25	18	15	3	144	0	2	140	
89	5	11	4	7	55	0	½	40	After
91	10	9	5	3	111	0	1	40	
91	15	9	9	0	167	0	1½	35	
82	32	18	19*	0	178	0	2	92	
98	2	2	1	1	100	0	½	35	Mann-Williamson operation
94	10	6	5	0	167	0	1	35	
68	28	17	16	1	155	0	1½	35	
77	39	23	23	0	169	0	2	112	
94	7	5	4	2	116	0	½	35	
91	9	9	5	4	100	0	1	34	
93	11	7	5	1	167	0	1½	34	
50	24	11	14*	0	218	0	2	175	
94	5	6	3	3	83	0	½	37	
94	10	6	5	0	157	0	1	37	
94	12	5	7*	0	200	0	1½	38	
95	12	4	7*	0	300	0	2	324	

Results Before and After Operation on Dog 5. The acidity values were determined only by titration with brom-cresol purple, not by determination of the acid chloride. Asterisk marks samples in which there was marked water absorption from the gastric contents.

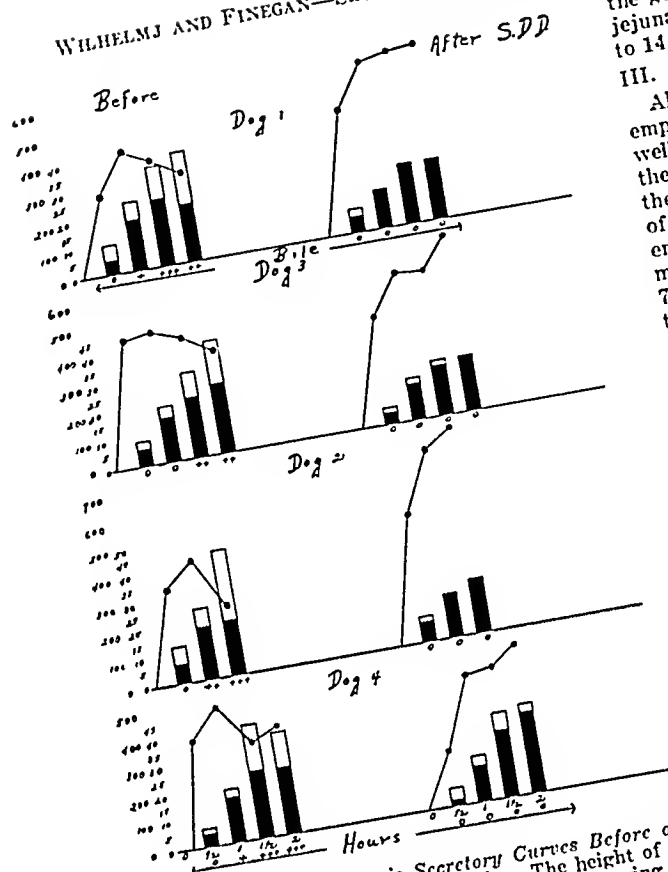


Fig. 1. Average Gastric Secretory Curves Before and After the Mann-Williamson Operation. The height of the rectangles shows the cc. of total secretions entering the stomach per 100 cc. of gastric contents. The black portion represents the cc. of acid secretion and the white portion the cc. of non-acid secretion. The line represents the milligrams of acid chloride per 100 cc. of secretion. The scale increasing by 5 indicates the milligrams of acid chloride per 100 cc. of secretion. + and zero signs refer to bile in the gastric contents as determined by the Pettenkofer reaction.

surprising that intestinal contents containing small amounts of bile could enter the stomach in two of our experiments. 3. In previously reported studies (8) the Mann-Williamson operation was performed but instead of anastomosing the duodenum into the terminal ileum it was drained into the jejunum by a large side to side stoma several inches below the gastro-jejunostomy. In such a preparation large amounts of bile and non-acid secretions were often found in the gastric contents, thus offering conclusive proof of the regurgitation of jejunal contents into the stomach.

These facts make it appear practically certain that the non-acid secretion was from intestinal contents in these unusual curves appearing in the stomach. It appears that this tendency is much more marked in some dogs than in others, since 5 out of the 9 experiments occurred in the same dog (dog 4), and this is seen to influence the average curve shown in Fig. 1. In some dogs curves of this type were never encountered. It is quite likely that regurgitation of intestinal and duodenal contents into the jejunum just below the gastro-jejunostomy, in some dogs, is one important factor responsible for

the great difference in the time of appearance of the jejunal ulcer after the Mann-Williamson operation (2 to 14 weeks) (9).

III. Gastric Emptying Time After Operation.

All animals showed a definite prolongation of the emptying time of the stomach after operation. This is well demonstrated in dog 5 (Table 1) by comparing the average volume of the last samples removed from the stomach before operation (33 cc.) with the volumes of the last samples after operation. This great difference existed in spite of the fact that the volume of test meal administered was reduced from 900 cc. before to 700 cc. after operation. This difference in emptying time was not caused by mechanical narrowing of the gastro-jejunostomy stoma, a fact verified at autopsy, but was quite likely the result of a spastic contraction of the jejunum which received the acid gastric contents. A similar prolongation of emptying time has been noted by other investigators (9, 10, 11) and Ivy (12) agrees that it is probably the result of jejunal spasm.

IV. The Acidity of the Gastric Contents Before and After Operation.*

In spite of the fact that the acidity of the total secretions entering the stomach was much higher after operation than before, the acidity of the gastric contents was practically unchanged or was slightly lower after operation. Two factors are responsible for this contradictory finding. First, in dogs 3 and 5 the emptying time of the stomach was so greatly prolonged after operation that in spite of a reduction in the amount of meal administered (900 cc. before—700 cc. after), the amount of meal remaining in the stomach to dilute the gastric secretions was much greater than before operation. The dilution of the gastric secretions by the test meal after operation was proportionately greater than the increase in the acidity of the secretions, hence the acidity of the gastric contents was slightly lower after operation than before. Second, in dogs 1, 2 and 4 it was possible to eliminate the factor of greater dilution of the gastric secretions by reducing the meal from 900 cc. before to 500 and 600 cc. after operation. This maintained about the same average amount of meal in the stomach before and after operation. This is shown by the average volumes of the last samples removed which were 35, 38 and 29 cc. before and 33, 48 and 72 cc. after operation. In spite of this, however, the average acidity of the gastric contents was almost the same before and after operation and it is obvious that some regulatory mechanism was in operation which controlled the acidity of the gastric contents. It appears quite certain that the regulatory mechanism responsible was that of acid inhibition. Previous studies have shown that as the acidity of the gastric contents rises the amount of acid secreted is progressively decreased. Acid inhibition thus appears to be an automatic mechanism controlling the acidity of the gastric contents independently of the acidity of the gastric secretions. Acid inhibition may also have been active in dogs 3 and 5 but because of the greater dilution of the gastric secretions by the test meal its role cannot be determined with certainty.

V. Absorption of Water From the Gastric Contents.

In previously reported studies on whole stomach pouches (1) in which the amount of non-acid secretion

*The acidity of the gastric contents is shown by the black portion of the rectangles in Fig. 1 and in column 2 of Table 1.

is small (13), we have shown that absorption of water from the gastric contents often occurs to such an extent that the amount of non-acid secretion may fall to zero while the apparent acidity of the pure acid secretion may rise considerably above the value determined by Hollander (14) (600 mgs. of acid chloride per 100 cc. or 0.170 normal acid). After the Mann-Williamson operation when no intestinal secretions regurgitated into the stomach similar changes were often found (Table I). In one experiment each on dogs 1, 2 and 5, water absorption became so marked that we observed a definite rise in the acidity of the gastric contents with an actual concentration of the per cent of phenol red to values ranging to 114 per cent of the value in the meal. Such observations can only be explained on the basis of absorption of water but not of acid from the gastric contents. Water absorption with concentration of the acid in the gastric contents may become so pronounced that the calculated amount of acid secretion may exceed the amount of total secretion. This is illustrated in Table I in the samples marked with an asterisk. It is quite likely that this process is going on to a variable extent at all times in normal dogs but is overshadowed by the regurgitation of relatively large amounts of non-acid secretions from the duodenum.

DISCUSSION

The above experiments show that the primary changes which occur in the gastric secretory curve after the Mann-Williamson operation are due to the fact that duodenal regurgitation is prevented. The curves of secretion after operation are almost identical with those previously found in whole stomach pouches

(1) and this similarity verifies a fact previously demonstrated (13), namely that the non-acid secretions of the stomach itself are too small in amount to cause any significant lowering of the acidity of the gastric secretions, unless the acid secretion is very small in amount.

Duodenal regurgitation and acid inhibition which are in operation simultaneously in the intact animal are dissociated after the Mann-Williamson operation and this separation has allowed us to determine the exact role played by each in the regulation of gastric acidity.

The present experiments justify the following statement regarding the role of these two mechanisms: The primary effect of duodenal regurgitation is to lower the acidity of the total secretions (gastric plus duodenal) entering the stomach; the acidity of the gastric contents may or may not be lowered depending upon the amount and acidity of the gastric contents in relation to the amount of secretions regurgitated from the duodenum. The acidity of the gastric contents is controlled primarily by the mechanism of acid inhibition. When acid inhibition occurs the acidity of the secretions is not influenced. Thus these two mechanisms are seen to play separate and distinct roles.

The above findings probably explain the results of Baird, Campbell and Hern (15) who found that the acidity of the gastric contents, after a gruel meal, was not changed by continuous aspiration of the duodenum which was stated to prevent regurgitation of duodenal contents into the stomach.

McCann (10) studied dogs before and after the Mann-Williamson operation and stated that there was no change in gastric acidity after operation. It is im-

TABLE II

Per Cent Phenol Red	Mgs. Acid Chloride secreted per 100 cc. gastric contents	Total secretion cc.	Acid secretion cc.	Non-acid secretion cc.	Mgs. Acid Chloride per 100 cc. gastric secretion	Bile	Time Hours	Remarks
94	13	6	2	4	216	0	½	Fecal masses in resting stomach and in gastric sample during test.
91	32	9	5	4	356	0	1	
74	98	26	16	10	378	0	1½	
64	130	36	22	14	361	0	2	
81	61	19	10	9	321	0	½	Fecal material regurgitated into stomach during test.
67	143	33	24	9	433	0	1	
93	35	7	6	1	500	0	½	Fecal odor of gastric contents.
80	100	20	17	3	500	0	1	
66	140	34	23	11	411	0	1½	
53	167	47	28	19	356	0	2	
91	52	9	9	0	578	0	½	Positive test for bile in last sample.
89	70	11	12	0	636	0	1	
70	136	30	23	7	453	0	1½	
26	118	74	20	54	160	+	2	
93	25	7	4	3	357	0	½	Positive test for bile in last sample.
82	70	18	12	6	359	0	1	
64	172	36	29	7	477	+	1½	

Five experiments after the Mann-Williamson operation in which considerable amounts of non-acid secretions entered the stomach. The presence of fecal material or faintly positive Pettenkofer tests indicate that the non-acid secretions regurgitated from the intestine into the stomach.

portant to note that McCann studied the acidity of the gastric contents only, his methods not permitting him to study the acidity of the secretions.

Orndorff, Fauley and Ivy (9) also found only slight increases in the acidity of the gastric contents after operation. However, they noted that there was a marked continuous secretion and hypersecretion as evidenced by a high prolonged secretion continuing from 6 to 8 hours after a meat test meal. This is probably due to a prolonged intestinal phase since hypersecretion was not observed in our animals in which the experiments lasted only two hours and were therefore terminated before the onset of the intestinal phase. According to Ivy (12) this prolonged intestinal phase is not found in all dogs after operation.

Several of our dogs were studied through the phase of ulcer development, up to the time of perforation, but no changes were found in the gastric secretory curve which could be ascribed to the presence of the ulcer.

These studies are in agreement with those of McCann (10) in showing that the jejunal ulcer following the Mann-Williamson operation develops with an acidity of the gastric contents which is essentially normal.

Previous studies (8) have shown that if the jejunum is supplied with the secretions of the duodenum it will

apparently resist ulcer formation indefinitely. It would be interesting to know whether human cases of duodenal ulcer show changes in the gastric secretory curve which are similar to those found after the Mann-Williamson operation.

SUMMARY

1 Following the Mann-Williamson operation the acidity of the total secretions entering the stomach is much higher than before operation. During the gastric secretory curve the acidity of the secretions continues to rise and does not show the normal terminal decrease. The non-acid secretions entering the stomach are either very small in amount or absent. These changes are due to the absence of duodenal regurgitation.

2 The emptying time of the stomach is markedly increased after operation due apparently to jejunal spasm.

3 The acidity of the gastric contents shows little change after operation.

4 Evidence is presented which indicates that the acidity of the total secretions (gastric plus duodenal) entering the stomach is controlled primarily by duodenal regurgitation while the acidity of the gastric contents is controlled primarily by acid inhibition.

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Review of Recent Practices in the Field of Gastro-Enterology at the University of Minnesota Hospitals

By

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THE development of gastro-enterology has been so rapid and complex in the past decade that a periodic review is helpful to glean the worthwhile from the outmoded practices. Accordingly the principles and practices in gastro-enterology at the University of Minnesota Hospitals are analyzed from the points of view of relating the diagnostic methods and forms of treatment that have proved most successful in our hands and of summarizing the different lines of research that are being carried on in this elude.

ULCER OF THE STOMACH AND DUODENUM

A Treatment by bile salts. During the past year Dr. Bergh of the Surgical Department has used bile salts (Bilron, Eli Lilly, gr V to X qid) in the therapy of benign gastric and duodenal ulcers with encouraging results. While our series of cases is small and the

mechanism of action is not understood, it appears that the administration of bile salts may prove to be a valuable adjunct in the therapy of ulcer.

B Acute perforation. Acute perforations of the gastro-intestinal tract rank high among the abdominal emergencies seen in this hospital. We have been interested in the factors influencing the development of peritonitis in these cases. In a general way the mortality from peritonitis following perforation of the gastro-intestinal tract depends on the number and virulence of the escaping organisms, which in turn depends on the size of the perforation, the length of time the perforation remains open, the number of organisms at the level of the perforation, the amount and fluidity of the material in the viscus at the time of perforation, the forces tending to carry the contents of the viscus out into the peritoneal cavity, etc. Al-

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the general and local resistance of the host are important.

Drs. G. S. Bergh, W. F. Bowers and O. H. Wangensteen have established experimentally perforations at different levels of the gastro-intestinal tract of dogs. Most of the perforations consisted of unsutured linear incisions, one centimeter in length. The mortality following perforation of the empty stomach was 6.9%, but when the stomach contained food, the mortality rose to 86.7%. Injection of a sclerosing solution into the stomach wall before operation delayed closure of the opening and the mortality in fasting animals was increased to 40%. (Compare with mortality of perforating cancer of stomach in human cases). In the small intestine the mortality was 81.2% following duodenal perforations, 44.4% following jejunal perforations, and 100% following perforations of the terminal ileum. The mortality following perforations of the large bowel in dogs was 23.1%. The importance of having the gastro-intestinal tract empty or seeing that it is made empty as soon as the diagnosis of perforation is made is apparent from this study.

C. *Diagnosis and treatment of acute perforated peptic ulcer.* Our practice in cases of suspected perforated peptic ulcer is to immediately insert an indwelling duodenal catheter and apply suction. If the patient is dehydrated from vomiting or poor fluid intake, he is given intravenous saline solution. In cases of perforated ulcer seen at this clinic shock is not a prominent feature until the terminal stages.

After physical examination of the patient with a suspected perforated ulcer, X-ray plates are taken to determine the presence of free gas in the peritoneal cavity. Three films are taken: a flat (scout) film with the patient supine, an upright and a left lateral decubitus film (to visualize gas under the right lateral wall). If the stomach is full of gas, and no free gas is seen in any of the three plates, suction is again applied to the intlying catheter and the intragastric gases removed. One should not be satisfied that there is no free intraperitoneal gas present under the dome of the left diaphragm until this is done. The following experience has occurred in this clinic: a case of suspected perforated ulcer showed only a dilated stomach on fluoroscopic and X-ray examinations. However, on removing the gas from the stomach, free gas was demonstrated under the left diaphragm. Subsequent operation disclosed a perforated duodenal ulcer.

D. *"Forme fruste" type of ulcer perforation of the stomach.* Cases of suspected perforated ulcer with no free gas demonstrated in the peritoneal cavity have been regarded on occasion as the "forme fruste" type and have been treated conservatively (4 cases). The patients made an uneventful recovery. However, no hard or fast rules can be made in the treatment of such cases. Just how certain one is of the diagnosis from the history and physical findings decides whether the treatment is to be surgical or conservative in this "forme fruste" type.

The question arises as to how little gas is required to be visualized in the peritoneal cavity and what percentage of cases of perforated ulcer show pneumoperitoneum. Three out of four cases of perforated ulcer in this clinic show free gas in the peritoneal cavity. As little as 5 cc. of air injected under the diaphragm of human beings may be visualized by X-ray (Paine and Rigler).

E. *Bleeding peptic ulcer.* It is said that bleeding peptic ulcers never perforate. However, in this hospital three cases of bleeding peptic ulcer have perforated while the patients were under strict medical management.

In bleeding ulcers suction applied to an indwelling gastric tube is employed as part of the conservative treatment. By keeping the stomach empty, there is less chance of perforation due to distention of the stomach with blood; the bleeding has a better chance of being controlled as the stomach is contracted, and there is less danger of masked hemorrhage into the lower gastro-intestinal tract. Such suction has apparently not increased the bleeding in these cases.

THE GALL BLADDER

A. *Conservative treatment of certain types of gall bladder disease.*

In this clinic uncomplicated cases of acute cholecystitis are treated by means of bed rest, hot packs to the abdomen, sedatives, suction applied to an indwelling duodenal tube, and paroral fluids. About six to eight weeks after the acute symptoms have subsided, cholecystectomy is performed if X-ray studies show evidence of poor emptying of the gall bladder and stones. There have been no deaths in any of the cases treated in this manner.

Also cases of chronic cholecystitis with no roentgenologic evidence of stones in the gall bladder or clinical evidence of common duct obstruction are treated conservatively by means of bile salts and low fat diet. Dr. A. G. Rewbridge of this Department has presented indirect (X-ray) evidence that stones in the gall bladder may be dissolved by bile salts.

B. *Studies on the physiology of the gall bladder.* Dr. E. A. Boyden, Department of Anatomy, University of Minnesota, and co-workers have made some interesting observations on the physiology of the gall bladder. Boyden and T. M. Berman found that in a study of 33 ulcer patients, the rate of evacuation of the gall bladder was markedly increased. This was considered to be due to the increased acidity or motility of the stomach in these patients. Also, Boyden and W. P. Ritchie found that the emptying time of the gall bladder in patients after gastric resection was normal. Dr. Maude Gerdes and Boyden found that in pregnant women the emptying time of the gall bladder is longer than normal which is probably an etiologic factor in the production of cholelithiasis in pregnant women.

Drs. J. A. Layne and Bergh have investigated the effect of distention on the common bile duct of unanesthetized patients. They find that distention of the common duct by water introduced through a T-tube (previously inserted at time of exploration for common duct stone) causes pain in the epigastrium or right hypochondrium in all cases; this pain is referred to the interscapular and right subscapular region in 50% of the cases. Apparently the same effect is obtained from spasm, presumably at the sphincter choledochus.

C. *Cholangiograms.* In all suspected cases of common duct stone, cholangiograms are made routinely at the time of operation. The cystic duct is isolated and clamped, and then into the common duct a No. 22 needle is inserted and 5-10 cc. of diodrast is injected. General anesthesia is used; drop ether or nitrous oxide is given while the X-ray pictures are taken. While the film is being developed, the diseased gall bladder is re-

moved. If the cholangiogram is negative, the results of manual palpation of the common duct as well as the clinical history determine whether the common duct is to be explored.

D. *Differentiation between obstructions of the common duct due to malignancy and stones.* In patients with obstructive jaundice, to differentiate between obstructions of the common duct due to cancer and malignancy the quantitative determination of the amount of urobilinogen in the feces has proven most helpful. Dr. C. J. Watson of the Medical Department has found that normally one excretes up to 200 mg. of urobilinogen in the feces daily, and none or only traces in the urine. In a series of obstruction of the common duct due to carcinoma, usually in the head of the pancreas, he found that the obstruction tends to be complete in that there is no urobilinogen in the stool. In his experience, the obstruction has rarely proven to be complete over a four-day period in cases of common duct stone. In this clinic this test has proven to be the single most valuable aid to date in differentiating between obstructions of the common duct due to malignancy and stone.

SMALL INTESTINE

A. *Diagnosis and treatment of intestinal obstruction.* In 1931, Wangensteen was first to treat a case of acute mechanical intestinal obstruction conservatively by means of continuous suction transmitted through an indwelling duodenal tube. Since then his ideas regarding intestinal obstruction have been widely recognized. A book has been written dealing with the recognition and treatment of intestinal obstruction as practiced at this clinic; hence the different phases of ileus will be presented only briefly in this paper.

The symptoms of intestinal obstruction are intermittent, crampy, colicky pain, nausea and vomiting. Physically, the patient may be markedly dehydrated from vomiting. The abdomen is distended; visible peristalsis may be seen. If the obstruction is of long standing, a "ladder" arrangement of the intestinal coils may be seen through the abdominal wall. The obstructing mass or distended loop may be felt. If the bowel is strangulated, the abdomen is more tender and rebound tenderness may be present. On auscultation one hears borborygmi in mechanical obstruction; in paralytic ileus, the abdomen is silent.

Routinely a scout X-ray film and an upright film are taken as soon as the physical examination of the patient is completed. While the X-ray film is the single most valuable laboratory method one has in the diagnosis and treatment of intestinal obstruction, if one does not view the roentgenograms in the light of the history and physical findings, the procedure may be more confusing than enlightening. Normally gas is never seen in the small intestine of adults; this is probably due to the small size of the gas bubbles and their intimate mixture with food in the small gut. Up to three years, one sees gas in the small bowel of children by X-ray as a normal occurrence.

In this clinic, cases of simple acute mechanical intestinal obstruction are treated by an indwelling duodenal catheter drainage with constant suction. In such cases suction accomplishes everything that an enterostomy does without the risk of operation. However, the condition of such patients treated conservatively must be constantly watched. The degree of distention must be checked by scout films every 12 hours at the least.

The only patients with small bowel obstruction whom we are afraid not only to treat but also that we may treat conservatively are cases of intussusception and obstruction due to impacted gall stones in the bowel. Since the latter condition is usually associated with a cholecysto-intestinal fistula, the presence of gas in the biliary tree may give a clue as to the obstructing mechanism (Rigler-Borman). In general, if the patient with suspected, simple, acute mechanical intestinal obstruction does not improve with suction applied to an indwelling duodenal catheter, some complication is present and one should not temporize too long with conservative measures. In such cases, the patient should have an abdominal exploration: If an adhesive band is found, simple cutting of the band may suffice. However, if the bowel is markedly distended, whether or not the obstructing mechanism is found, it is usually best to perform just an enterostomy. In intestinal obstruction, the importance of asepsis in the technique of enterostomy has been stressed by Wangensteen. At this clinic, the enterostomy tube is left in situ for 10-12 days in most cases of ileus; on removing it, the sinus tract closes promptly. About four to six weeks after the patient has recovered from the intestinal obstruction, a gastro-intestinal study is performed, giving barium sulfate by mouth. If no intrinsic pathologic process is found and the most likely cause of the ileus was intraperitoneal adhesions, no further surgical treatment is advised. However, if this patient has repeated attacks of ileus, an abdominal exploration and enterolysis may be in order.

In strangulating obstructions and occlusions of the colon, conservative therapy is contraindicated. To be certain, one cannot always tell what the exact obstructive mechanism is, but from the history, physical findings, and X-ray evidence, one is usually able to tell: 1, if there is an obstruction present, 2, whether the obstruction is simple or strangulating in character, and 3, whether the large or small bowel is involved. To those of us who have been schooled in the uses and limitations of suction siphonage in the treatment of intestinal obstruction, there is no doubt that in physiologic obstructions and incomplete mechanical ileus due to adhesive bands suction applied to an indwelling duodenal catheter is far superior to any surgical procedure. In other obstructions where the diagnosis is not so certain, while the employment of suction may be used, disaster may follow if constant vigilance is not given to changes in the patient's condition.

APPENDICITIS

A. *Experimental studies.* In 1847, Gerlach described an inconstant semilunar fold of mucous membrane guarding the appendico-cecal orifice. Buirge and Wangensteen in a study of 526 specimens found that while folds may be present around this orifice, there was no indication of a sphincter muscle at the site of union of the appendix and cecum.

Wangensteen and Bowers found that there is a fecolith in the lumen of the appendix in about half the cases of acute appendicitis. The possibility that appendicitis is a form of intestinal obstruction was at once suggested. However, the fact that only about half the cases of acute appendicitis showed signs of organic obstruction suggested that other factors,

possibly functional obstruction, might cause acute appendicitis.

Wangenstein, Buirge, Dennis and Ritchie found that the vermiform appendix exhibits a definite resistance to luminal perfusion. This resistance depends on the amount of circular muscle in the wall and the diameter of the lumen; also, it varies from hour to hour and can be modified by certain drugs. Adrenalin tends to stop the contractions of the appendix, while atropine, benzydine and papaverine have an inconstant effect. Morphine tended to raise the basal pressure and increased the frequency of the smaller waves but decreased their size. B-methyl acetyl choline increased the size and frequency of the small waves as well as raised the basal pressure.

The above authors also found that the obstructed appendix may secrete 1-2 cm. of fluid a day. The nature of the fluid is still obscure. Of the laboratory animals studied so far, only in the rabbit is obstruction of the cecal appendage accompanied by the secretion of the fluid. In fact, in the rabbit, in 10-14 hours, the intraluminal pressure of the appendix obstructed by a ligature increases so much, due to fluid production, that rupture occurs. When croton oil is administered by gavage or hypertonic saline solution injected intravenously, rupture of the obstructed appendix of the rabbit occurs in a much shorter time.

Knowing that the appendix may become easily obstructed, that the appendix does secrete fluid, and from our knowledge of closed-loop obstruction, the pathogenesis of acute appendicitis becomes clearer. The effects of age and the minute anatomy of the appendix as they bear on the problem of acute appendicitis are discussed by Wangenstein et al.

B. Conservative treatment of certain forms of appendicitis.

At this clinic all uncomplicated cases of acute suppurative appendicitis are treated by immediate appendectomy. However, if there are signs of localized abscess or generalized peritonitis, it is our practice to treat such patients conservatively and operate when the acute infection is well subsided (8-10 weeks later). If the patient has been sick for 3-4 days, his temperature over 101°, the pulse over 120 per minute, and the clinical findings not entirely confined to the right lower quadrant, he most likely is treated conservatively, although each case has to be individualized and no hard or fast rules can be made. If the patient comes in with a well localized abscess in the right lower quadrant the patient is treated conservatively; if the mass gets smaller, the conservative treatment is continued; however, if the mass gets larger or the temperature fails to return to normal after three or four days, the abscess is drained. No attempt is made to remove the appendix until 2-3 months later.

The mortality of our cases of appendicitis treated conservatively and surgically have been summarized by Myrick and Sperling. In our hands, cases of ruptured appendix with abscess formation or generalized peritonitis have responded best when treated conservatively. Particularly in certain cases of appendicitis in children has this proven true. Adams and Baneroff of the Pediatric Department of this hospital found that of 110 cases of ruptured appendicitis with abscess formation or generalized peritonitis in children

under 14 years, treated conservatively, only 5 died (4.5%).

LARGE INTESTINE

A. *Diagnosis and treatment of large bowel obstruction.* Colonic obstructions differ both clinically and in their treatment from those of the small bowel. Patients with large bowel obstruction rarely vomit until late in the disease; aspiration of the stomach contents in these patients does not reveal gastric retention or fecal regurgitation as in small bowel ileus. The danger in colonic obstruction is that if complete the segment proximal from the obstruction to the ileocecal valve acts as a closed loop (Sperling) and may perforate at its weakest point, the cecum. These patients should not be treated solely by suction applied to an indwelling duodenal tube but by a preliminary colostomy.

In obstructions of the colon, a marker (a five-cent piece) is fastened to the umbilicus by adhesive tape and a scout film of the abdomen is taken. The marker gives an idea of the location of the obstruction as well as serves as a unit of measure. To decompress the bowel, a transverse incision to the right or left of the upper midline of the abdomen is made; this approach is preferred as the exploration of the whole colon is easier. The colon will present itself directly into the wound, and evisceration is less likely to occur. At this clinic since the above procedure has been used, there has been a great improvement in the operative mortality of colonic obstructions. If the obstructing carcinoma should be in the region of the sigmoid, a secondary operation of the Bloch-Mikulicz type will have to be performed later.

B. *Prolapse of the rectum.* In the treatment of prolapse of the rectum, Wangenstein has found a modification of the Whitehead operation for hemorrhoids to be most satisfactory. With the patient in the lithotomy position, the rectum is allowed to prolapse to its fullest extent. Just proximal to the mucocutaneous junction, a circular incision is made excising only the mucosa to the apex of the prolapse. The mucosa at the apex is then sutured to that near the mucocutaneous juncture. In the few cases done to date, the results have been very satisfactory.

C. *Posterior excision of colon carcinoma.* For carcinoma of the colon below the peritoneal reflection, the procedure in this clinic has been largely to perform a left inguinal colostomy and later do a posterior excision of the lesion. For lesions 6-8 cm. above the peritoneal reflection the posterior excision has often been done where others would have preferred the abdomino-perineal operation. Removal of these higher lesions can often be done from below even though the procedure is somewhat time-consuming and without the far greater risk of the combined operation.

PRE- AND POST-OPERATIVE CARE

A. *Prophylaxis against peritonitis.* In operations upon the stomach, the importance of having the stomach empty has been stressed. The night before operation, an indwelling suction catheter is inserted through the nostril and left in the stomach so that the stomach will be empty at the time of operation. Also, the patient is encouraged to sip dilute hydrochloric acid through a glass tube (10 cc. N HCl in 200 cc.

water). Cultures taken from the stomach through the nasal tube have been found to be sterile for as long as

1½ hours after taking the acid. The value of this procedure as a prophylaxis against peritonitis is apparent.

At the time of operation, the opened bowel surfaces are swabbed with sodium ricinoleate 1%, and at the end of the operation, three or four ounces of this solution are often left in the peritoneal cavity. Experimentally, we have found this solution to be a better germicide and to prevent adhesions more often than ether, amfetin, papain, etc.

B. *Prophylaxis against post-operative complications.* After most laparotomies, the patient is encouraged to move his arms and legs frequently and to turn from side to side as a prophylaxis against thrombophlebitis and hypostatic pneumonia. Also as a preventative against atelectasis, holding the costal margin of the patient and encouraging him to cough is invaluable. Hyperventilating with CO₂ and O₂ mixtures has been discontinued because of the expense, lack of uniformity in administration, and because the above procedures are simpler and more effective. Breathing into a paper bag held tightly against the face is also an effective means of hyperventilation. Thyroid extract is not used here as a prophylaxis against thrombophlebitis; in fact thrombophlebitis has been seen to develop spontaneously in cases of severe hyperthyroidism. To prevent post-operative parotitis, the patient is encouraged to use mouth wash, suck lemons and chew gum. If parotitis develops, the use of hot packs to the involved region seems to be just as effective in our experience as radiation therapy or the oral administration of Lugol's solution.

C. *Use of suction applied to an inlying duodenal tube.* We have come to use suction siphonage by nasal catheter in many conditions other than intestinal obstruction. For instance, it is used preoperatively in all cases of surgery of the stomach or bowel, and in cases where a collapsed gastro-intestinal tract facilitates the operative procedure as splenectomy, operations on the pancreas, ventral hernioplasty, etc. Post-operatively, it is invaluable in the treatment of paralytic ileus. After two surgical procedures the onset of paralytic ileus is particularly insidious: thoracoplasty and the application of a body case in hyperextension. It has been our experience on the Chest Surgical

service that if immediately after thoracoplasty the patient has a high pulse and low blood pressure, he is in shock, but if he has a high pulse but normal blood pressure, he may have acute gastric dilatation.

In the conservative treatment of ruptured appendix, suction applied to an indwelling duodenal catheter tends to keep the small bowel empty, thereby preventing paralytic ileus as well as more contamination of the peritoneal cavity. Also, there is a better chance for the inflammatory process to be walled off as the bowel is quiet.

In ulcer patients with night pain, suction applied to an indwelling gastric tube lessens the pain by removing the hydrochloric acid from the stomach.

The question arises as to how long one may use suction siphonage. Suction has been applied to an indwelling duodenal catheter (inserted through the nostril) for as long as 7-10 days continuously and as long as 23 days intermittently. The patients suffer little discomfort except for sore throat which can be relieved by gargles or 10% cocaine topically applied to the throat. The fluid intake and output of all patients with duodenal suction must be carefully computed, making sure the patient has a positive fluid balance. The plasma chloride must be maintained by intravenous saline solution, and the plasma proteins by blood transfusions. The ionic equilibrium in patients being treated by suction siphonage is being investigated by Paine and Armstrong. The possibility of constructing a tube to both feed and aspirate the patient has been suggested.

SUMMARY

The above review is a broad rather than a detailed survey of our present diagnostic methods and forms of treatment. An attempt has been made to present time-proven rather than "new" procedures. The result of further study and clinical experience will undoubtedly modify many of them.

Some of the commoner problems of gastro-enterology as the etiology of peptic ulcer, pathogenesis of gall stones, prevention of peritonitis, etc., still await final solution. Periodic reviews and the interchange of ideas between various clinics will do much to clarify these problems.

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The Management of a Permanent Colostomy*

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THE proper management of colostomies will enable the majority of patients to forget the discomforts of an abdominal anus for more than twenty-three hours a day. In cases in which the artificial anus is in the cecum, ascending or transverse colon, this is neither easily nor often achieved. Fortunately, however, most permanent colostomies are located on the left side and permit this comfortable state to be readily attained. The return to normal life may be so complete that one may be acquainted with an individual for years and yet never be cognizant of the fact that he has an abdominal anus. People in all walks of life have resumed their usual occupations. There are others, however, less fortunate, who lead miserable existences in constant fear that an unexpected movement may embarrass and inconvenience them and betray their misfortune to all about them. Many of these patients can be rehabilitated economically and socially, but ignorance of that possibility, or the method of its accomplishment, or both, keep them from the physical and mental comfort that should be theirs.

Differences of opinion exist among physicians as to the proper methods of controlling the preternatural anus. Many rely solely on the colostomy bag; others prefer absorbent dressings which are changed as often as necessary. Many and varied gadgets have been invented in an attempt to "cork up" the colostomy for periods of time. Some physicians purge their patients one day and depend upon the resultant temporary constipation to keep their patients comfortable. Great stress has been placed on training the patient to form a regular bowel habit, on diet, on irrigation, and on all three combined.

In the follow-up clinic of the colonic service at The Mount Sinai Hospital, an attempt was made to determine the best methods of caring for the colostomy patient and to establish a standard routine procedure. The knowledge acquired in the care of this type of patient and a review of the more recent literature is the subject matter of this paper. The discussion follows under six headings:

(1) Diet, (2) Medication, (3) Irrigation and training, (4) Use of appliances and dressings, (5) Care of the skin, (6) General measures.

1. DIET

Diet undoubtedly plays the major role in the proper management of a colostomy. The object of dietetic control is to obtain a constipated patient who will have an evacuation only on taking an irrigation. The diet prescribed should produce a stool which is hard, dry, formed, and scant in amount. We have found the most successful diet to be the bland low residue diet with low fat and high carbohydrate components.

Any food which has an irritating action on the stomach or bowel should be avoided. Condiments,

alcohol in any form, iced drinks and charged water, all of which may produce gastro-intestinal disturbances and hyperactivity, are not permitted. Certain foods such as prunes and apricots are forbidden because of their laxative action. Any food which cannot be considered bland should at first be deleted from the list of edible foods.

The diet should be low in residue and foods which produce bulk in the stools must be scrupulously avoided. The vegetables and fruits permitted should be well cooked to render the cellulose as soft and as thoroughly digestible as possible. Initially, these should be pureed. Any food which is indigestible, such as the seeds of berries and the tendinous parts of meat, should never be taken because of the irritating residue.

The low fat diet is employed because it has been found to be the most constipating. Schmieden (1) limits fats until the colostomy is functioning satisfactorily. Hesse (2) believes that intestinal action may be stimulated by a diet rich in fats and accordingly he also limits fats. Cattell (3) starts his patients with a bland diet, low in fat, and later includes a moderate amount. Dubois (4) suggests that at first all foods containing considerable fat should be avoided. In spite of the fact that these patients have lost considerable weight which they should regain and although difficulty may be encountered in administering high caloric meals without the inclusion of fat in the diet, we believe it beneficial to start with the low fat diet. The advantages of comfort and cleanliness resulting from proper bowel control more than counterbalance the difficulties and disadvantages of the diet. Furthermore, the administration of a high carbohydrate diet augmented by chocolate, cocoa, and sugared drinks during meals will increase the caloric intake sufficiently to result in a substantial gain in weight if all other factors are conducive to this.

We have not routinely attempted to limit the fluid intake of our patients. Schmieden and Hesse do so in an effort to produce dry and more constipated stools. We have not found this limitation necessary in left sided colostomies, but it may occasionally be a useful adjuvant in the care of a right-sided or transverse colostomy. There is no doubt also that within certain limits, less food will produce less stool. For this reason Dubois (5) recommends abstinence as being of great advantage in simplifying the care of a colostomy. We, however, have found it unnecessary to limit the quantity of food, and encourage the patient to eat enough to maintain an excellent state of nutrition. Limitation of food and fluid may be attempted occasionally in the obstinate case which does not respond favorably to the usual means of control.

Regular meals and a complete abstinence from food between meals should be the rule. The patient who nibbles at food between meals is most likely to be the one who finds small amounts of stool on the dressing several times a day. Whenever practical, water should

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be taken only at meal time inasmuch as it may incite the gastrocolic reflex.

THE INITIAL COLOSTOMY DIET

The following foods are recommended:

Vegetables—Cooked vegetables with soft cellulose. (Potatoes, carrots, squash). Vegetable puree. (Peas, beets, string beans, tomatoes, asparagus tips).

Fruits—Cooked fruits with skins and seeds removed. (Apple, pear, peach). Strained juices. (Orange, grapefruit, tomato).

Breads and Cereal—White bread and plain crackers. Cooked fine cereals. (Cream of wheat, pabulum, patent barley, rice). Ready-to-serve cereals without bran. (Corn flakes, puffed wheat). Spaghetti, noodles, macaroni. Plain cake without icing.

Dairy Products—All milk must be boiled. Swiss and American cheese. Small amounts of butter. Eggs—Boiled or poached.

Meats—Tender, well cooked meat, fish and chicken. Fat and tendinous parts should be avoided.

Desserts—Cake or fruit as above. Clear fruit jelly. Simple bland desserts. (Cornstarch, chocolate or tapioca pudding. Custard, junket, plain gelatin).

Miscellaneous—Cocoa, chocolate, weak tea. Caffeine-free coffee or postum if necessary.

The following foods should be avoided:

Vegetables—All vegetables except those listed above. Any raw vegetable. Irritating vegetables. (Onions, peppers, radishes). Vegetables high in residue.

Fruits—Raw fruits. Fruits high in indigestible cellulose. (Pineapple). Fruits containing many seeds. (Berries).

Breads and Cereals—Whole grain breads. (Whole-wheat and pumpernickel). Cereals high in residue. (Bran cereals, wheatena).

Dairy Products—Cream, cheeses other than those listed above.

Meat—Pork, veal or duck. Skins of poultry. Fatty and fibrous parts of meat.

Miscellaneous—Fried foods of any kind. Jams. Spices and condiments. Highly seasoned or strongly salted foods. Coffee, strong tea, charged water, alcohol in any form.

A typical diet follows:

Breakfast—Fruit juice or fruit. Well cooked cereal with boiled milk and sugar. Eggs. White bread or toast with butter or jelly. Cocoa or chocolate.

Dinner—Tomato juice. Meat, fish or chicken. Boiled, baked or mashed potato. Pureed vegetables as listed. Fruit or pudding. White bread or toast. Cocoa or tea.

Supper—Milk soup with strained vegetables or clear soup. Meat or cheese or eggs. Vegetables. Custard or pudding or gelatin. White bread or toast with butter or jelly. Cocoa or tea.

Shortly after the desired degree of constipation is obtained, new foods may be cautiously added. Only one new food should be given over any two day period, so that if it is deleterious, it can be immediately recognized and subsequently avoided. Individuals differ markedly in their reactions to food. Certain people will be constipated regardless of what they eat, whereas others may have a profuse diarrhea for twenty-four hours following the ingestion of a raw apple. There is a certain group of patients who have been constipated all their lives and who continue to remain so after operation. This group may eat almost

anything after a time without untoward effects on colostomy function. There are others whose frequency of bowel movement directly reflects the foods eaten. Proper diet will adequately constipate this group. There is still a third group who normally have two to three bowel movements daily. After operation this group presents a difficult problem and requires careful dietetic management, supplemented by proper medication, for the attainment of a well controlled colostomy.

The first change usually permitted is the serving of the whole cooked vegetable instead of the puree. This change may be made at a relatively early period. Later, raw skinned fruits and a greater variety of vegetables are added, and if these are tolerated well, cream or uncooked milk may be used in the cereal and tea. The allowance of butter is increased and the fatty parts of meat are given if desired. Fried foods are added last, if at all. Foods such as cabbage, celery, poultry skins and others which have an irritating or bulky residue should never be permitted except in those cases in which the degree of constipation is so marked that any food may be taken without materially affecting the bowel function. Additions are continued until the patient is receiving the maximum number of foods that is compatible with the desired degree of constipation. It is obvious that the ultimate diet will vary greatly in different patients because of their individual reactions to foods.

2. MEDICATION

Although most of our patients lead comfortable colostomy lives without the aid of constipating medications, there are certain patients who require them and are materially benefited by their use. The patient with a transverse colostomy who despite careful attention to diet still has loose stools, may be greatly helped by the proper medicines. The nervous individual often requires constipating medication and small doses of sedatives for successful regulation. The judicious use of drugs is indicated when patients are first attempting to constipate themselves. Finally, they may be temporarily necessary after a dietary indiscretion.

Bismuth subcarbonate in doses of 15 to 60 grains, three times a day, is valuable in inducing constipation or allaying diarrhea. Dubois states that not only does it tend to make the stool more solid but also renders them odorless. It also diminishes the amount of gas in some patients. Powdered kaolin, a somewhat less constipating medication, may occasionally be used along with, or instead of the bismuth.

Opium is very often efficacious when other drugs fail, but it should be used over relatively short periods of time. It may be administered simultaneously with other medications. The two most used preparations are tincture of opium in doses of five, ten, or twenty minims, three or four times daily, and paragoric in teaspoonful doses at like intervals. The amount of morphine administered is relatively small, the former containing 1/10 of a grain of morphine in each 10 minims, and the latter containing 1/40 of a grain of morphine to each four cubic centimeters.

Charcoal is often advised as a remedy for excessive amounts of gas. Sollmann (6) claims that whereas freshly heated charcoal adsorbs gasses, moist charcoal does not possess this quality and that it is,

therefore, unsuccessful in the treatment of flatulence. Schmieden reports that it not only rids the patient of gas but also deodorizes the stools. Hesse speaks highly of animal charcoal for similar reasons. We have found that finely divided and dried vegetable charcoal occasionally reduces the amount of gas. It is administered in doses of 15 to 30 grains three times a day.

The use of Kerol to deodorize the excreta is recommended by Lockhart-Mummery (7) Shedden (8) and Best (9). A capsule containing 3 minims is given daily before breakfast.

Laxatives and purgatives are mentioned only to be condemned. They are rarely needed and do not fit into our scheme of the proper management of a colostomy. Constipation is the state we attempt to produce so that defecation of feces will occur every two or three days and then only under the stimulation of an irrigation. No one who has spent several hours with a colostomy patient suffering from diarrhea will need to be cautioned against the use of purgatives.

Occasionally one sees left-sided colostomy patients who do not respond to the constipating diet and medications. These patients may be suspected of having so called gastrogenous diarrhea due to achylia gastrica. Diagnosis is made of course by a fractional test meal. Rehfuess (10) states that even small amounts of hydrochloric acid will succeed in overcoming this diarrhea. The dilute hydrochloric acid may be used in liquid, capsule, or tablet form.

It is recommended that those patients who require a strict constipating diet over long periods of time be given concentrated vitamins, especially vitamin D to augment the scant vitamin content of the diet.

3. IRRIGATION AND TRAINING

Irrigations are of the utmost importance in the care of a colostomy. There are in the literature scattered reports about a chronic colitis that occurs following a long continued use of irrigations. Most observers, however, find irrigations an excellent procedure in the management of a colostomy and see no ill effects from its long continued use. Binkley (11) states that daily irrigation of colostomies has been in vogue for many years at the Memorial Hospital in New York and that experience has proven this procedure to be by far the most satisfactory method. Cattell, Smith (12), Bowman (13), and others, employ irrigations routinely. We have had excellent results from the irrigation treatment of colostomies and have so far never seen ill effects. The object of the irrigation is to thoroughly empty the colon of its fecal content so that no movement will occur during the intervals between irrigations. The length of these intervals is determined by trial and error. It will be found that patients who are chronically constipated prior to operation will often be able to allow two or three days between irrigations. This may also be true for those who are able to achieve a marked degree of constipation by means of diet and medication. Constipation in patients with colostomies has not been found to be detrimental to the general health. The average patient requires an irrigation about once in twenty-four hours. We employ the simplest possible technique. An ordinary enema bag or can is equipped with a tube, a shut-off valve, a glass adapter and a 26 F. catheter. Warm tap water is used for the irrigation which may be given with the patient sitting, standing, or lying

in bed. The enema can is placed about three feet above the level of the colostomy, the catheter is inserted into the colostomy as far as it will go, and the water is allowed to flow in slowly. A large deep basin is held snugly against the abdomen just below the colostomy to catch whatever may run back along the catheter. Sometimes it is necessary to hold a piece of gauze or cotton tightly against the lumen of the bowel to prevent too much loss of water. When the patient feels quite full, the catheter is removed and the water and intestinal contents are expelled into the basin. When all the water and stool have seemingly been expelled, the entire procedure is repeated once or several times until the return is clear. About ten to twenty minutes are allowed to elapse before the permanent dressing is applied because during this time fluid temporarily retained in the colon will be discharged. A small piece of gauze and a large thick cellulocotton or cotton pad is placed over the stoma to absorb the fluid as it is expelled. Later the permanent dressing is applied. Further attention is usually not required for the ensuing twenty-four hours.

This is the so-called "open" method of irrigation. With a little care and practice it can be performed with no soiling of the body, clothes, or room. The average time required is about forty-five minutes. The only parts of the apparatus requiring cleaning are the catheter and basin. There is, however, a "closed" method of irrigation for which numerous devices have been invented. Best (14) employs a metal urinal which has a tube running into it near the handle and out through the mouth of the urinal. This tube is inserted into the colostomy, the urinal is held firmly against the abdomen over the stoma, and the water is allowed to flow through the tube, wash out the colon and run back into the urinal. Binkley uses an excellent apparatus for closed irrigation. It consists of a bakelite cup which has a small opening for a catheter and a wide outlet which connects with a broad soft rubber tube. The cup is held in position over the stoma by an adjustable canvas belt. The apparatus can be used with the patient lying in bed or sitting on toilet. The irrigating fluid is run into the colon through the catheter and the returning fluid and feces is expelled into the cup and conveyed through the wide rubber tube into a receptacle or into the toilet unseen by the patient. Binkley has found this method so satisfactory that he uses it routinely.

For the fastidious or sensitive patient, one or another of these appliances may be found very useful. The advantage of the closed method lies solely in its aesthetic appeal. Its disadvantages are: the apparatus itself must be cleaned, the irrigation takes longer, and the continuous irrigation with the catheter in place does not clean the bowel quite as well as the intermittent flushing and emptying.

There is a small percentage of patients who do not need to employ irrigations but are able to have a regular movement every morning and remain perfectly clean for the remainder of the day. Many more patients are able to have the regular movement but tend to have several very small movements during the day. Gibson (15) prefers irrigation to training. Lockhart-Mummery attempts to train his patients to have regular movements before inaugurating irrigation treatment. Schmieden and Hesse advocate training. Webb (16) employs small irrigations at

first for the purpose of establishing habitual morning evacuations. The individual who is fortunate enough to have this automatic function is to be encouraged provided that he is able to remain perfectly clean for a full day between movements. The method of starting this movement varies with the individual. Some find that the thought of a movement is sufficient to initiate it; others find that a glass of cold water or hot coffee, or a cigarette may cause the bowel to function. In our experience very few patients are able to remain perfectly clean for twenty-four hours without irrigations.

4. USE OF APPLIANCES AND DRESSINGS

Colostomy bags are rarely prescribed. They are never employed for left-sided colostomies but are used exclusively in the occasional cecostomy or transverse colostomy when these cannot be controlled by the usual methods because of the impossibility of obtaining solid stool. The use of colostomy bags for left-sided colostomies is fast falling into disrepute. Almost all who have written upon this subject attempt to discourage their use. The colostomy bag is a highly unsatisfactory appliance which is difficult to clean and to keep clean. It is usually expensive and requires frequent renewal because of the offensive, musty, odor which the rubber retains and emanates. It causes irritation of the stoma and the surrounding skin and deforms the normal contour of the patient. Binkley, Gabriel and Lloyd-Davies (17), Best, Landsman, (18) and others call attention to the frequent abdominal wall weaknesses and ventral herniae seen about the stoma among those who are addicted to colostomy bags. It is not certain whether these are caused by ischemia from the pressure of the rim of the bag, or whether it is due to the suction effect of the bag. The protrusion of the bowel all too frequently seen in these cases, is due to the suction effect and presumably the more frequent movements are likewise attributable to the same cause. There is no doubt that prolapse and ventral hernia occur among those who do not wear colostomy bags, but the incidence is very much less. Furthermore, we have seen patients develop both hernia and prolapse months after discharge from the hospital after they were fitted with a colostomy bag by their physicians. Prior to this they had repeatedly been examined in the follow-up clinic and found to have neither hernia nor prolapse. It is also true that a low grade inflammation of the exteriorized mucous membrane is often seen in patients wearing colostomy bags. The thick mucus that is discharged constantly from these colostomies is very distressing and quite frequently produces a dermatitis of the surrounding skin. One needs only to watch the offensive messy spectacle of a patient changing and cleaning the bag in order to be thoroughly disgusted with it. Colostomy bags should never be used except as a last resort when all else fails.

For the few unfortunates who require a colostomy bag, it is advisable to secure one possessing several important qualities. It should be, if possible, inexpensive so that a new one may frequently be obtained. The cup fitting over the stoma should have a small diameter so as not to produce herniae. The straps should be detachable and washable. The contrivance

should be relatively flat in order that it may not cause too great a bulge and distortion of the patient's figure. It is sometimes helpful to insert gauze or cellulocotton into the colostomy bag, to absorb the fluid and so make the wearer more comfortable and the cleaning easier. Whenever possible, the physician himself should select the bag.

The simplest possible dressing is employed. After the temporary dressing previously described is removed, it is replaced by the permanent dressing. The exposed bowel is covered with a strip of gauze on which boric acid ointment or vaseline has been applied. Another piece of gauze is placed over this and a pad of cotton or cellulocotton is then applied. Some patients like to have "lap straps" on either side of the abdomen to tie over this; others merely wear their supporting belts. A piece of oiled silk may be interposed between the belt and the dressing. Most patients wear a belt and all are encouraged to do so. A simple belt made of elastic webbing is often quite satisfactory. These are inexpensive and are usually made by the patient. They have some tendency to roll at the sides and are at times productive of post-prandial pressure and discomfort. An adjustable abdominal support made of knitted elastic, narrow over the sides and back, and broad in front, with two or three pliable vertical supports anteriorly, has been found most satisfactory. Some patients have in addition, a simple elastic belt or muslin binder which is used at night.

5. CARE OF THE SKIN

The usual left-sided colostomy causes a negligible amount of skin irritation and little, if any, care of the skin is necessary. Occasionally, however, the skin will become inflamed and even ulcerated. This is seen far more often in the presence of cecostomies than in any other large bowel neostomy. In the prevention and treatment of dermatitis, any ointment which adequately protects the skin from the irritant to which it has been subjected may be used. The ointment we have found to be the most efficacious is made of ten per cent zinc oxide and ten per cent finely powdered aluminum in anhydrous lanolin. This is applied on the thoroughly cleaned and dried skin all about the stoma and the usual dressings applied. It is of great importance that the patient keep watching for the first signs of dermatitis, because when it is moderately advanced, it is quite difficult to cure. It is advisable to use an ointment constantly if the stoma discharges liquid stool, irritating stool or much mucus.

Occasionally patients report bleeding from the stoma. Closer questioning will often disclose that the blood was seen to issue from the junction between the skin and mucous membrane. Inspection reveals some granulation tissue which is easily and successfully treated by the application of strong silver nitrate solution.

Rarely a patient will return with some stenosis of the colostomy opening. A moderate degree of stenosis without definite retraction of the loop of bowel leading to the opening is not harmful and should merely be kept under observation. If the contraction continues, it may become necessary to dilate the opening manually or with bougies, preferably after the infiltration of novocaine. If, however, there is a marked degree

of stenosis, with or without retraction of the spur, surgical therapy is indicated.

6. GENERAL MEASURES

Before discharge from the hospital, the patients are taught how to irrigate themselves. Upon leaving the hospital they are given printed directions for the proper method of open irrigation, a list of foods to be eaten, a list of foods to be avoided, and a typical diet. Some patients are visited at their homes by a nurse who instructs the patient and some member of the family in matters appertaining to colostomy care.

At first, patients visit the clinic at short intervals, and diet and regime changes are made as indicated. After the patient is well regulated, he is seen at intervals of four to six months. He is weighed, his general condition is noted, a search for distant metastases is made, and the colostomy is carefully inspected for local recurrence, stenosis, retraction of the spur, prolapse and hernia.

Some patients are able to exercise violently without encountering any difficulty, whereas others may have a small movement after moderately severe exertion. It is necessary to determine the patient's reaction to

exercise by trial and error and to act accordingly. Most patients do this by themselves a short time after discharge from the hospital.

Individualization is the key note of success in the management of a colostomy. Patients vary in their approach to the problem of colostomy life just as they vary in their reactions to other problems. One patient will accept the colostomy calmly and follow instructions willingly, whereas another will speak of suicide, refuse to do anything connected with his care, and require an attendant for months after his wounds have healed. The methods which may be applied on the first patient can never be employed on the second. Each patient must be considered as an individual problem and the routine varied accordingly. The mental attitude of the patient must be considered and carefully schooled in the proper channels. Infinite tact and patience are required in caring for these patients to whom the colostomy comes as a severe shock and a loathsome disfigurement. In time, with proper guidance of thought and action, the colostomy may become just another one of the many burdens that the individual patiently carries with him throughout life.

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Notes on a Trip to Scandinavian Countries and London

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SCANDINAVIAN COUNTRIES

COPENHAGEN.—One of my most valued experiences was making the acquaintance of Prof. Knud Faber. Dr. Faber is seventy-six years of age and has now retired. He has been, and still is, one of the outstanding medical figures in the Scandinavian countries. He retains his interest in things medical and is head of the Dansk Tuberkuloselaegeselskab. He has shown that the increased incidence of tuberculosis during the World War was inversely related to the supply of foods such as meat and butter.

He first published his observations on gastritis in 1898, and he has been responsible for placing gastritis on a firm pathologic basis. He does not believe that the term "hypertrophic gastritis" is important unless actual polypoid changes are present. He stated that the symptomatology of superficial, ulcerative gastritis

resembles that of peptic ulcer, and in his hands the treatment has been much the same. He uses lavage with salt water and sometimes hydrogen peroxide if other measures do not cure. My impression was that he does not regard atrophic gastritis or gastritis with anacidity as such a clear-cut clinical entity as superficial ulcerative gastritis. He believes the symptoms are largely owing to associated disturbances in the function of the bowel—particularly constipation—and he directs much of his treatment to care of the bowel. He uses dilute hydrochloric acid, not so much because he feels that there is need for replacement therapy but because the patient seems often to progress better when it is given.

Professor Faber is opposed to the use of surgical measures in cases of ulcer if it can be avoided because he has seen so many patients who were worse after surgical intervention.

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Commune Hospital. Here, I made the acquaintance of Prof. H. I. Bing, who is a charming man of sixty-six. He has a great deal of enthusiasm and was spoken of with affection by physicians in Copenhagen. He very courteously showed me his hospital which was built about 1866. He is physically fit and never rides in an automobile. He still rides his bicycle at a fast clip and some time after I left the hospital he proudly overtook me, remarking that there was a lot in the old man yet.

Professor Bing is a physician of the old school and believes strongly in the practice of clinical medicine in preference to laboratory medicine. His extraordinary skill in the art of percussion and palpation was obvious, and its development has constituted one of his major interests. From this has developed his observations on what he terms "viscerocutaneous or axonal" reflexes. He demonstrated for me by percussion the contracture of the colon and of the stomach following irritation of the skin overlying these organs, and of the changes in location of the borders of the lung following scratching of the skin of the thoracic wall.

I remarked that the art of examining the patient by percussion and palpation as he had demonstrated it was fast becoming a lost art. He laughed and said, "Yes, I often say that I am the last of the Mohicans!"

In Professor Bing's clinic I was happy to meet his assistant, Dr. Thune Anderson. Anderson has made important observations on the etiology of epidemic jaundice and has most interestingly shown that the epidemic and endemic types of jaundice are related to a comparable disease occurring in hogs. He has transmitted the disease from hog to hog by feeding infected livers, and he has transmitted it from man to hog by feeding to the hog bile obtained by drainage from patients with epidemic jaundice. This observation on the etiology of epidemic jaundice is an important one to the Danes, who fear that it may well affect the export of bacon to England, one of their main sources of revenue. This problem is receiving the attention of the medical profession as well as of economists of the country.

Bispebjerg Hospital. Here, I saw Prof. E. Meulengracht, who is best known in this country for the Meulengracht test or the icterus index, and because he has advocated immediate feeding of patients with bleeding peptic ulcer. Actually it is unfortunate that most of the physicians of this country do not know that they owe the icterus index to Meulengracht. His wards are well run, and it would be well worth while for anyone going to Copenhagen to visit them. He still believes in feeding the patient who has a bleeding ulcer. I saw many of these patients in his wards and they certainly seemed to be doing just as well as do those of our patients who are given a limited diet. From the moment these patients enter the hospital he gives them five good-sized meals of puréed foods a day, and any amount of fluid they desire. As a result of this treatment, he feels that the period of convalescence has been shortened and dehydration and emaciation have been avoided. He also believes that he has lowered the mortality rate to 1 or 2 per cent. He stated, however, that the differences in mortality rates in different countries might be owing to the fact that there may be differences in the severity of the lesions. Certainly, the severity of the hemorrhage in his wards was not great.

Meulengracht has made contributions to the problem of pernicious anemia. He showed that the anti-anemic principle is to be found chiefly in those parts of the stomach and duodenum which are lined by the cardiac glands, the pyloric glands, and the glands of Brunner. Recent study of the duodenums of patients with pernicious anemia has shown, however, that Brunner's glands are well preserved. Professor Meulengracht is not able to explain this unless it be that these glands supply an inadequate amount of the intrinsic principle.

Meulengracht believes that the treatment of peptic ulcer is primarily a medical problem, and surgical measures are seldom resorted to. Gastro-enterostomy is then the operation of choice.

Amtssygehuset Genofte is one of the county hospitals. It is a relatively new hospital. The medical service here was in charge of Dr. Tage Christiansen, and the type of medicine being practiced certainly was as good as that seen in any of the teaching city and university hospitals. Dr. Christiansen is energetic and has a forceful personality. Christiansen follows Schindler in his conception of gastritis. He thinks that gastritis begins in the fundus and spreads distally; that superficial, ulcerative gastritis responds well to treatment and that the hypertrophic form may or may not be associated with ulceration. He thinks that in a small percentage of cases this superficial ulcerative gastritis goes over into the atrophic form. He believes that gastritis and gastric ulcer are two distinct diseases etiologically and pathologically.

One of my reasons in looking up Dr. Christiansen was because of his interest in and knowledge of pancreatic disease and of pancreatic function. His studies were begun with the hope of developing a method for the diagnosis of pancreatic disease. He used predigested food as a stimulant, but finally concluded that while his work was of physiologic interest it did not have wide application clinically, because of the variability in results brought about by mechanical factors incident to duodenal distention.

Christiansen agreed with Dr. Meulengracht that the treatment of ulcer was primarily a medical affair and he resorts to surgery in only a few cases. Then gastro-enterostomy is the operation of choice.

Stockholm.—On my arrival in Stockholm I got in touch with Dr. I. Holmgren. He is now professor emeritus, but he still maintains many of his old interests. He is editor of the "Acta Medica Scandinavica" and has been in a great measure responsible for the fact that medical papers are now being written in English; this gives the Scandinavian writers a much wider influence in the world. Many of the English and American textbooks of medicine are now being used in Sweden without translation.

Serafimer Lasarettet Hospital. Professor Holmgren arranged for me to meet Prof. Nana Svarts, who is in charge of the medical service at this hospital. Ordinarily, there are two professors of medicine in Stockholm, but at the present time Professor Svarts is the only one because of the recent death of Professor Jacobæus. Dr. Svarts is a woman and so far as is known, is the only woman in the world who is a professor of medicine.

She has long been interested in fermentative diarrheas, which she treats with autogenous vaccine and colonic irrigations composed of a weak solution of kollargol, together with a low carbohydrate diet. She

has also been interested in ulcerative colitis and has found a variety of organisms in the stools. A diplococcus has been found, but she does not feel that this is the only organism responsible for the disease. She treats patients with a vaccine, a high carbohydrate, high fat and somewhat bland type of diet, irrigations with kollargol, and the usual vitamins. Many cases of this disease are sent to her for treatment.

Dr. Svarts stated that in the treatment of arthritis they do not place the same emphasis on focal infection as we do in this country. The treatment of hyperthyroidism differs somewhat from that used here. Surgical operation is resorted to when the patient is young and radiation is employed later in life. The results of roentgenologic treatment are said to be good.

On Dr. Svarts' service the diagnosis of gastritis is based on the visualization of the mucosal pattern by roentgenologic methods. Nothing new is being used in the treatment of the condition. Again, peptic ulcer is looked on as a medical disease, the indications for surgical measures being "three cures, two hemorrhages, or one episode of obstruction." The operation of choice for many years has been gastric resection, usually of the Billroth II type. Professor Svarts, however, felt that there was a distinct tendency now to go back to gastro-enterostomy.

One of the chief things I wanted to find out while in Stockholm was something about the value of peritoneoscopy. Professor Jacobaeus, who died last year, had used this for many years. Dr. Svarts stated that his enthusiasm for this method of examination had waned during the years and that during the last five years of his life he had used it only in cases of ascites, wherein he wanted to determine the cause in liver or peritoneum. His enthusiasm for the thoracoscope did not wane; he used it for cutting adhesions preparatory to collapsing the lung in cases of tuberculosis and for localizing tumors.

Sankt Eriks Sjukhus Hospital. Prof. Hilding Berglund is in charge of the fourth medical service at this hospital. His service is well organized and he has as his assistants, Dr. Bengt Ihre, Dr. Henrik Lagerlöf and Dr. A. Rune Frisk.

Dr. Ihre has shown that small amounts of hydrochloric acid can be demonstrated in almost every case of apparent achlorhydria if continuous suction of the gastric contents is carried out following the injection of histamine. He has also shown that when the vagus nerves are stimulated by giving 16 units of insulin intravenously, the injection of histamine, intramuscularly, will produce some secretion of some free hydrochloric acid in an even greater percentage of apparently achlorhydric patients. Ihre is also studying gastric acidity in its relation to gastritis. He thinks that there are variations depending on the condition of the mucous membrane. Dr. Ihre has been doing gastroscopy for some time and has much skill in this technic.

The dietary management of the bleeding gastric or duodenal lesion is usually a liberal one in Stockholm just as it is in Copenhagen.

If the patient is not vomiting, food and fluids are given freely. The treatment of peptic ulcer is again thought to be essentially medical.

Dr. Lagerlöf has been responsible for the clinical application of secretin in the study of pancreatic function. At Dr. Berglund's suggestion he carried out a test for me, and showed that secretin obtained from

animals will produce a flow of pancreatic juice in man. By using a double tube with one opening in the stomach and the other in the duodenum, he prevented gastric secretion from entering the duodenum and secured almost pure pancreatic juice, at least from those patients with a competent sphincter of Oddi. Secretin increases especially the volume and the alkaline content of the pancreatic juice. On the other hand, the concentration of the enzymes is more markedly influenced by stimulation of the vagus nerves by insulin or pilocarpine. Food likewise increased the concentration of enzymes in the juice. Dr. Lagerlöf agreed that probably in the future, it will be found best in testing pancreatic function to use secretin and pre-digested food together as stimulants. He insisted, however, that the use of secretin alone could disclose major and minor variations in the functional and secretory capacity of the pancreas.

ENGLAND

It is always stimulating to visit the great London hospitals.

London.—Guy's Hospital. Sir Arthur Hurst's Tuesday afternoon clinic was attended. Two cases were of especial interest; the first was one of chronic intussusception of an adult in examination of whom a sausage-like tumor could be palpated in the right upper quadrant of the abdomen. There had been a long history of intermittent obstruction. The second case was one in which malnutrition was the chief symptom. The patient had undergone gastrojejunostomy many years previously. After repeated roentgenologic examinations, a gastroduodenal fistula was demonstrated. Exploration had revealed only a very small, sinus-like tract, the narrowness of which explained the difficulty the roentgenologists had had in demonstrating its existence. Sir Arthur believed that the long pre-operative preparation of the patients was a factor in the low mortality rate which he attains in these cases. He cleans out the bowel and uses a low residue diet.

Hammersmith Hospital. This is a part of the University of London postgraduate Medical School. The medical service under Professor Fraser and Reader Aitken is excellently organized. A case of multiple, tuberculous strictures of the bowel with a blood picture of pernicious anemia was presented as an illustration of the rôle which defective absorption can play in the production of macrocytic anemia. A full-blown case of scurvy was also seen with, strange to say, a negative tourniquet test.

Hospital of Tropical Diseases. Dr. M. Hamilton Fairley showed many interesting cases of sprue and atypical avitaminosis. In his experience, tropical sprue responds much more favorably to the administration of liver extract than does nontropical sprue. Dr. Fairley's pathologic studies on cases of sprue have led him to discard the theory that atrophy of the mucous membrane is responsible for the lack of absorption of fat and proteins in this condition.

Note: It is always interesting to hear at first hand what's new medically in foreign countries, and it is particularly interesting to hear from a traveler and particularly from a traveling gastro-enterologist whose interests are our own. Because of this we would be happy to publish from time to time in the columns of this Journal, interesting accounts of medical observations made abroad.

Dr. Mandred Comfort has just returned from Europe, and I have asked him to tell us here briefly of his experiences in the Scandinavian countries and in London.

—The Editor.

A Leader in Gastro-enterology Says . . .

"The recent advances in gastro-enterology have been of such magnitude and distinction that they engender in us a just pride and renew our determination to press forward toward our goal of perfection."

Dr. Ernest H. Gaither, Baltimore, Md., in his address at Kansas City before the section on gastro-enterology and proctology of the A.M.A.

The American Journal of Digestive Diseases

- Now in its fourth year of publication—without alteration in its fixed principle of giving to the reading members of the medical profession the contributions of the best clinicians and investigators in the United States, Canada and Europe.
- So formulated, and edited by one of the most capable and select editorial groups in contemporary medical journalism, the Journal has made unusual progress during the comparatively short period of publication . . . today, the editorial office is constantly in receipt of very valuable manuscripts which collectively form a cross section of new gastro-enterological thought.
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STUDIES ON THE PARALLEL ACTION OF VITAMIN C AND CALCIUM	Simon L. Ruskin, M.D.
THE PASSAGE OF GALL STONES THROUGH THE SPHINCTER OF ODDI	Marie Ortmyer, M.D. and Margaret Austin, M.D.
INFRA-RED PHOTOGRAPHY OF THE ABDOMINAL WALL IN PORTAL CIRRHOSIS OF THE LIVER	I. R. Jankelson, M.D. and Henry Baker, M.D.
THE EFFICIENCY OF SEVERAL GERMICIDES AND ANTISEPTICS ON THE ORAL MUCOSA	Esther Meyer, Ph.G., M.S. and Lloyd Arnold, M.D.
PRIMARY CARCINOMA OF THE LIVER	Abel Levitt, M.D., F.A.C.P. and Dexter S. Levy, M.D.
THE USE OF HYDRATED MAGNESIUM TRISILICATE IN PEPTIC ULCER (PRELIMINARY REPORT)	Manfred Kraemer, M.D., F.A.C.P.
VARIATIONS IN THE LEVEL OF SERUM LIPASE IN EXPERIMENTAL PANCREATITIS	Hamilton Baxter, M.D., Stewart G. Baxter, M.D. and John F. McIntosh, M.D.
COD LIVER OIL PER RECTUM AS AN ADJUNCT IN THE TREATMENT OF ULCERATIVE COLITIS	R. Russell Best, M.D.
THE RELATIONSHIP OF THE DIET TO THE SELF-REGULATORY DEFENSE MECHANISM. I. HYDROGEN-ION CONCENTRATION AND BACTERIAL FLORA	Nicholas P. Sullivan, M.S. and Ira A. Manville, M.D., Ph.D.
HEALTH AND NUTRITION OF HIGH ANDEAN INDIANS	Clarence William Lieb, A.M., M.D.

An Open Letter to the Physicians of North America

Do you realize that 60 per cent of all symptoms in general practice arise from the digestive tract?

Many diseases are intrinsic, and many at a distance reflect their symptomatology with great facility in the alimentary canal . . .

Is diagnosis of digestive diseases easy?

Apparently not. The old rule of thumb—"appendix, ulcer, or gall bladder" is no longer useful. We are becoming gradually acquainted with the disorders and diseases of the colon and reducing this information to some semblance of order. Physiology, bacteriology, chemistry, parasitology, clinical observation, animal experimentation, roentgenology, nutrition, allergy and psychology are the organized methods of approach to a fuller knowledge of

digestive diseases. And there still lies beyond, the dark continent of the small intestine, concerning which so little is positively known.

To the scholar, what is offered by this Journal is indispensable.

To the man too busy to indulge his yen for applied research, may we say this—an hour a month with the American Journal of DIGESTIVE DISEASES will provide the key to practical success in this most important, difficult, but "treatable" field.

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Editorials

ANNOUNCEMENT

AFTER the death of Doctor Smithies, the American Journal of Digestive Diseases carried on somewhat experimentally under a board of four editors. Although these individuals worked devotedly, they were much handicapped by not having a chairman to direct and correlate their work.

To repair this defect Doctor Cornell and the American Gastro-Enterological Association have now agreed that there be an editor-in-chief, acceptable to both contracting parties and working always in close cooperation with the Council of the Association, to take control of the editorial and advertising policies. This seemed to be the surest way of attaining the end so much desired by both Doctor Cornell and the Association, namely, the building of the Journal into as fine, dignified, scientific, and practically useful a magazine as it is possible to make.

This means that while Doctor Cornell's office will continue to be responsible for the financing of the Journal and its assembling, printing and mailing, the supplying of material for it is now up to all of us in America who are interested in the problems of digestion. All can work to build up this Journal, and all can take pride in what success is later attained. As the new editor, I can succeed only with your help and support. I am to be your servant, and especially during this first year I shall need and welcome your suggestions and criticisms.

As in the past, so even more in the future, the object of the Journal will be to supply helpful information on gastro-enterologic topics to physicians, surgeons, physiologists, laboratory workers, teachers of medicine, proctologists, dietitians, and all others who are interested in the problems of nutrition both in health and disease.

This Journal will continue to welcome manuscripts from anyone with a new and interesting message. Every effort will be made to keep short the interval between the reception of a manuscript and its appearance in print. We hope to have more articles and shorter ones, and we hope to present several times a year reviews of what is being done in the gastro-enterologic field in other lands. We hope also to publish in these pages reports of work of interest to gastro-enterologists that is done by men outside our ranks in physiology, surgery, dietetics, pediatrics and roentgenology.

Walter C. Alvarez, Rochester.

DR. A. C. IVY GETS THE GOLD MEDAL AT THE MEETING OF THE AMERICAN MEDICAL ASSOCIATION IN SAN FRANCISCO

ALL gastro-enterologists who for years have watched with interest the stream of valuable papers that have come from Dr. Ivy's laboratory in the Northwestern University Medical School will rejoice at his award of the Gold Medal given by the American Medical Association for the best exhibit presented at the recent meeting in San Francisco. The medal might well have been awarded for any one of several of Ivy's important discoveries of gastro-enterologic interest,

but actually it was given because of his production of hermaphroditic or intersexual rats by the prolonged injection into the pregnant mothers of large amounts of the newly isolated sex hormones. A study of the remarkable combinations of male and female characteristics in the pelvic organs of these animals must throw great light on the ways in which the sexual organs differentiate and develop in the normal male and female.

Another recent achievement of Dr. Ivy and his students was the demonstration that the removal of the stomach from growing puppies produces a severe homogenous osteoporosis. The animals become bowlegged, much as in rickets, but the disease is not rickets and it appears in spite of the fact that the animals are given plenty of calcium and vitamin D.

The deficient ossification seems to be due to three factors: (a) the absence of hydrochloric acid, which normally helps in the absorption of calcium from the bowel; (b) the loss of the reservoir function of the stomach and the resultant speeding of food transport through the bowel, and (c) the presence of a postcibal acidosis, or acid tide, which tends to decrease the retention of calcium (Bussabarger, Freeman and Ivy, A. J. P., 121:137-148, 1938).

Walter C. Alvarez, Rochester.

A NEW IDEA IN THE TREATMENT OF ULCER

AT the recent meeting of the American Medical Association in San Francisco, one of the most interesting and thought stimulating papers and exhibits was by David J. Sandweiss, H. C. Saltzstein and A. Farbman, from the Harper Hospital and the Medical Department of Wayne University, in Detroit. Doctor Sandweiss noticed that women with ulcer commonly lose their symptoms when they become pregnant. Searching through the literature, he and his associates found that this had been observed by a number of men. A review of 70,000 consecutive hospital records of pregnant women showed only one case in which note was made of an active ulcer. There were many notes made, however, of concomitant appendicitis and cholecystitis. In a group of forty-six women with ulcer studied carefully, it was found that only one had active symptoms of ulcer during pregnancy. Several of the women commented on the fact that the coming of pregnancy would always heal their ulcer. A rather high percentage of the women with ulcer were thought to have some signs of endocrine disturbance.

The possibility occurred to Sandweiss that the hormones found in the urine of pregnant women might be responsible for this beneficial action of pregnancy on ulcer. About 100 dogs were prepared according to the Mann-Williamson technic in which the duodenum is drained into the lower ileum and the first segment of jejunum is anastomosed to the pylorus. Of forty control animals, all died with large typical jejunal ulcers after an average of fifty-eight days. In 70 per cent of these control animals the ulcer perforated. Fifteen of these dogs were injected with theelin, which

seemed to aggravate the ulcer so that perforation and death took place more quickly than usual.

Forty dogs were then injected with the anterior pituitary-like hormone from the urine, and on the average these survived over 100 days. In 50 per cent of the animals necropsied there was no sign of ulcer, and in half of the remainder there were histologic signs of healing in the ulcer. In only about 15 per cent of the treated dogs did the ulcer perforate. When one remembers that Mann-Williamson dogs usually succumb to a perforated ulcer within two or three months, it is remarkable that seven of the forty dogs treated are still alive and well, most of them nearly a year after the operation.

Sandweiss and his coworkers then inactivated the anterior pituitary-like hormone by heating it four hours at 90° C. and injected ten Mann-Williamson dogs with this inactivated extract. Nine of these animals died with the typical jejunal ulcers.

The next question that occurred to Sandweiss and his associates was whether the urine of normal persons contained the protective substance. Actually, when the urine of normal, nonpregnant women was extracted according to the technic used in preparing the anterior pituitary-like substance, and when this extract was used in the treatment of ten dogs, it also was found to be protective. The workers then made a similar extract from the urine of men and women with ulcer, but when this was injected into Mann-Williamson dogs it seemed to do harm, and the ulcers became more destructive to life.

Sandweiss, Saltzstein and Farbman are careful to point out that because of the small number of animals used for the last described experiments, they cannot

yet be certain about the results; they are only suggestive.

Walter C. Alvarez, Rochester.

NEW HOPE FOR THE EPILEPTIC

ONE of the most hopeful and interesting announcements made recently is that of Drs. H. H. Merritt and T. J. Putnam of Boston, who have found a drug which is much more efficient in quieting the brain and preventing convulsive seizures than are the ones previously available. These workers took advantage of the fact that by certain operative procedures they can produce a disease in the cat which much resembles epilepsy. Using these cats as test objects, they tried one chemical substance after another until they found some that controlled the convulsions better than did bromides and phenobarbital. The best drug found in this way was diphenylhydantoin.

They now report that in 77 per cent of patients with a severe type of epilepsy, tested with the drug, the seizures were either completely prevented or else reduced in frequency. Very fortunately the drug is able to quiet the brain enough to prevent the attacks without at the same time causing unpleasant drowsiness.

Doubtless the drug will now be tried out extensively with the hope of relieving many other conditions in which the brain is abnormally irritable, and everyone will be keenly interested to see the results of these tests. If the usefulness of this new drug should prove to be as great in the hands of everyone as it has been in the hands of Drs. Merritt and Putnam, they will have earned a most honorable place in the hall of fame.

Walter C. Alvarez, Rochester.

Book Review

Chronic Intestinal Toxemia and its Treatment. By James W. Wiltsie. Baltimore, William Wood and Co., 268 pp., 1938.

MANY a gastro-enterologist has doubtless wondered if there is anything of value in the treatment of so-called chronic intestinal toxemia with colon lavage done in the office with special apparatus. Most men are predisposed against the procedure because it is based on an ancient theory of medicine which has been dragged out time and again in the last 4,000 years, only to be thrown back repeatedly into the junk room of medicine, and of course into the hands of irregular practitioners and laymen. It does seem that if the method had any real value it should have established itself in practice years ago.

Actually, this little book by Wiltsie seems to be the best written and best documented apology for colon washing that has as yet appeared. It is written by an earnest man with an M.D. after his name, obviously a man who wants to do the right and the scientific thing, and who has no sympathy with quackery. As he says on page 4, "The rather prevalent tendency to ridicule the use and users of colon irrigations naturally dampens the interest of anyone who otherwise might feel inclined to study their value. One brave enough to use them is apt to be regarded as either a fool or a knave. He is held under suspicion, ignored and avoided."

Unfortunately, as so often happens, the physician who goes against the better judgment of his fellows, gets to feeling that they are influenced and bound solely by taboos. As Wiltsie says: "It is surprising what influence a professional taboo of this nature has upon the mental processes of the individual members. They do not seem to be able to think independently or reason logically. Rather than accepting their training and education as an emancipation of thought, and feeling free to use their knowledge in constructive ways, they are restrained by authority and fear of ridicule. However, there is no place for creeds in medicine; but having satisfied the fundamental requirements of an adequate knowledge of the medical sciences, all that is required of us in the practice of our profession is intellectual honesty, moral integrity, and mature judgment."

After this statement, the reader will be the more inclined to reject the teachings of the book if he finds that Wiltsie is living and working by a creed, and if he finds him dodging and saying nothing about all the important facts that are against his theory.

Usually, a wise, well-trained physician with a large experience and good clinical judgment can tell after a quick look through a paper or a book whether or not the writer had the clinical and scientific judgment to walk warily in the narrow path between science and

pseudo-science. He can judge the author in a minute by the quality of his case reports, and he will damn him promptly if it is obvious that with his pet procedure he was trying to cure everything under the sun, or that while busy washing the colon, he failed to note that the patient had a gall bladder full of stones or an ulcer, or a manic depressive insanity, or just a plain, everyday neurosis. Thus, recently, the reviewer happened to see a patient who had had his colon washed strenuously for months by a well-known man with an M.D. after his name. It was not surprising that the patient didn't get well, seeing that his trouble was not in his colon but in his head. If the physician had been less busy colon-washing he would have noted the slight paralysis of the face, the slight aphasia, and the complete character change that followed a stroke.

Many of Wiltzie's case reports show that he realizes that every disease cannot be cured by irrigations, which is a tremendous step forward for a colon washer. Unfortunately, Wiltzie is not clear as to what the syndrome of chronic intestinal toxemia is. As he says on page 6, "Since this syndrome is not a well-defined entity, but presents different pictures in different individuals, pathognomonic signs and symptoms are not to be expected. The condition must first be suspected, then proved or disproved. If it is present we shall have little difficulty in checking the findings as of intestinal origin. In addition to purely subjective evidence, we may find anemia, abnormal blood-pressure, increased blood sedimentation rate, increase of the conjugated end-products of intestinal putrefaction in the urine, loss of weight, catarrhal conditions of the mucous membranes, specific blood agglutinins, etc. Singly, or in twos and threes, these findings mean nothing, but linked with others commonly found, the history of the case, subjective symptoms, etc., the presumption that our suspicions are justified will increase as the evidence multiplies. Improvement under therapeutic test forms the final link in our diagnostic chain."

One suspects from this that pretty nearly anything can be accepted by the colon washer as grist for his mill.

On page 18 Wiltzie says, "In all chronic toxemias and infections *I now proceed on the assumption that the colon is invariably involved*, (Italics are the reviewer's. This book looks a bit like a creed) and treat it regardless of the presence of other foci. In actual practice I have demonstrated, at least to myself, that it is better practice to treat the colon before attempting the removal of other known foci, since many of these will clear up spontaneously as soon as the colon is functioning normally."

This, of course, reveals the author as a bit more enthusiastic about his method than most gastro-enterologists could bring themselves to be. One could easily go through the book and show many instances of weak reasoning or of the quoting of scripture to a purpose. Many things Wiltzie says are self-evident would be pretty hard to prove to most physicians.

Another way in which one can quickly judge of a man's good sense and general trustworthiness is by watching to see how he chooses the authors whom he

quotes, and whether he quotes with equal confidence the pronouncements of unscientific men, whose work is not accepted by the medical profession, and of able and revered leaders in fields of research. Actually, Wiltzie would have greatly strengthened his argument by not quoting certain men as approvingly as he does.

The next question asked by the reader who is trying to form an opinion of an argument is: Did the writer face squarely every bit of evidence that was against his theory or did he ignore it? In this case, one immediately looks through the book to see if there is any adequate discussion of those scores of research articles on auto-intoxication which were summarized and evaluated in 1924 for "Physiological Reviews." How does Wiltzie face these many reports of laboratory investigations, nearly all of which failed to support the theory of intestinal auto-intoxication? Unfortunately Wiltzie does not even mention this outstanding article in his bibliography.

It has always been a puzzle to the reviewer what the difference is between an enema given to herself by a patient at home, and an irrigation given by a quack or a doctor in his office, and hence we are particularly disappointed in that the book does not clear up our doubts on this point. There must be a huge difference because one reads on page 234 the astounding statement that "the use of enemas during or following a series of irrigations should be strictly forbidden, not only because a pernicious habit may be acquired, but also because there is nothing better calculated to upset everything that colonic therapy is endeavoring to accomplish"! One would think from this that the most important thing Wiltzie could do is to show his readers exactly why an enema given at home is so dangerous and harmful and why one given in the office is so beneficial. We searched through the book for more light on this, the most important problem raised by the author but failed to find it.

There is some help on page 109, where Wiltzie quotes from Bastedo to the effect that, "the term irrigation conveys the idea of washing; therefore, while the ordinary enema is given with the purpose of inducing defecation, the irrigation is administered, not to induce defecation but to wash out material situated above the defecation area and to lavage the wall of the bowel as high as the water can be made to reach." This helps, but still we are left a little puzzled.

Of course, all theories aside, the final test of any method is what it can do. One must expect many persons to feel better while the colon is being kept clean but it is hard to see why there should be any permanency in the results after the irrigations are stopped.

If there is one disease which colonic irrigation might conceivably help, it should be chronic arthritis, but it would seem that Wiltzie's results in this field have been poor, because instead of bragging about them, he quotes from the writings of others, and suggests the use of vaccines.

We have here, then, a book written with much devotion and with more clinical acumen than is met with in most colon washers. But still the reviewer is not convinced that it would pay him to put in a colon washing table. Perhaps he is just getting old and "set in his ways."

Abstracts

CONNOTATIONS

H. J. SIMS

Denver, Colorado

Pohl, in 1737, gave a fairly accurate description of prostatic calculi. As late as 1838, Civalé stated: "Their origin is very dark; they have not been studied accurately enough so that it can be said under what pathological conditions they are formed, nor what

organic changes lead to their formation."

Biliary peritonitis of obscure origin was first reported by Saunders, in 1783. A fourteen year old boy, after falling from a tree was bled and purged for four days because of severe pains in the abdomen. His abdomen gradually enlarged and on the twenty-fourth day two gallons of

bile was removed through a trocar. On the thirty-seventh day he was again tapped. The trocar entered the intestine and he died of peritonitis five days later.

Drainage of the abdominal cavity as now practiced was developed after McDowell began performing ovariectomies. It was found in most of the fatal cases a collection of serosanguinous fluid formed in the pelvis.

Drainage through the cul-de-sac was first attempted by Keith, in 1864. He also introduced intraperitoneal drainage through the rectum. Celsus, so far as is known, first drained the abdomen for the removal of ascitic fluid. His tubes were made of lead and brass and tapered to prevent slipping into the abdomen. Galen, in the second century, and Avicenna, in the eleventh, used the same technique as Celsus.

Adenoma of the liver in young infants suggests the congenital origin of these tumors. Wagner, in 1861, described such an instance in a nursing.

The first detailed description of fibrous osteoma of the jaw was published by Menzel, in 1872. The tumor was noted by the patient over a period of twenty-five years. It was removed because of partial obstruction of the air and food passages.

Bennett, in 1881, exhibited before the Dublin Pathological society a series of fractures of the metacarpal bones. Such fractures are recognized as Bennett's fracture.

John Hunter transplanted cocks' spurs into their combs. The spurs grew to an enormous size. He attributed the excessive growth to inflammation, believing that an increase in the blood supply stimulated healing by giving power of action.

Diverticulosis of the colon was described by Cruveilhier, in 1849, Virchow in 1853, by Rokitsansky in 1856. These investigators are usually given credit, however, Ballies' Morbid Anatomy published in 1794, recognized sacculations of the colon.

Trephining for depressed fractures of the skull was done in ancient Egypt. Hippocrates observed that fractures with depression were not particularly dangerous unless the membranes were ruptured.

Lanza and Higgins were the first Americans to make a comprehensive report on silicosis. The disease is not a recent one for Ramazzini, in 1700 described the condition.

Richter, in 1778, gave a complete scientific description of a hernia which now bears his name. Treves



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ELKHART

INDIANA

suggested that this type of hernia be called Richter's hernia to differentiate it from the hernia of Littre.

WHYTE, DAVID AND O'REGAN, ROLLAND
Complete Prolapse of the Rectum.
New Zealand Med. Jour., 36:381-382, Dec., 1937.

The injection method of treatment of rectal prolapse is not entirely safe. A case is reported in which sloughing of the rectal wall occurred with severe and repeated secondary hemorrhage. Temporary colostomy and six blood transfusions in the course of seventeen days were considered necessary in treatment. The end result was complete cure.

Hanes M. Fowler, Fort Wayne

CARMALT-JONES, D. W.

Disorders of the Pituitary Gland in Relation to Circulatory and Metabolic Disturbances. Med. Jour. of Australia, 1:439-440, March 5, 1938.

Anterior pituitary excess leads to overgrowth, hypertension increase in basal metabolic rate, with at present an imperfectly traced influence on the other endocrine glands. No medication is of any service in these cases. A defect of the anterior lobe of the pituitary leads sometimes to wasting, sometimes to obesity and a low basal metabolic rate. Patients with these conditions may be capable of treatment with anterior pituitary extracts. Water metabolism is controlled by the hypothalamus and posterior lobe of the pituitary, and persons suffering from excessive loss of water may be treated by posterior pituitary extract.

Hanes M. Fowler, Fort Wayne.

CONNOTATIONS

H. J. SIMS
Denver, Colorado

Placenta accreta, a comparative rare condition was known to the older obstetricians. Morgagni made mention of the condition and commented that it was difficult even with a bistoury, to separate the placental tissue from the uterine muscle.

Ried, of Erlangen, a German surgeon, was the first to recognize tuberculosis of the flat bones of the vault of the skull. His article appeared in 1842, however, the cases were observed in 1838.

Carcinoma of the male breast was mentioned in the writings of Arcaeus (1493-1573). Hildanus (1537-1619) described a similar case. It was not until 1872 that a systematic study of this disease was made by Horteloup.

Le Gallois, in 1812, Knox in 1839, and Barlow in 1854, reported rupture of the symphysis pubis articulation in parturient guinea pigs, seals and cows.

Hahn in 1881, conceived the idea of sewing the perirennal fat to the walls of the lumbar incision. He named his procedure nehrorrhaphy.

In 1870, Gilmore made the deliberate and successful effort to remove a kidney during pregnancy.

The first case of iliopectineal bursitis was reported by Fricke of Germany, in 1834. Joly, in 1847, recognized the second case.

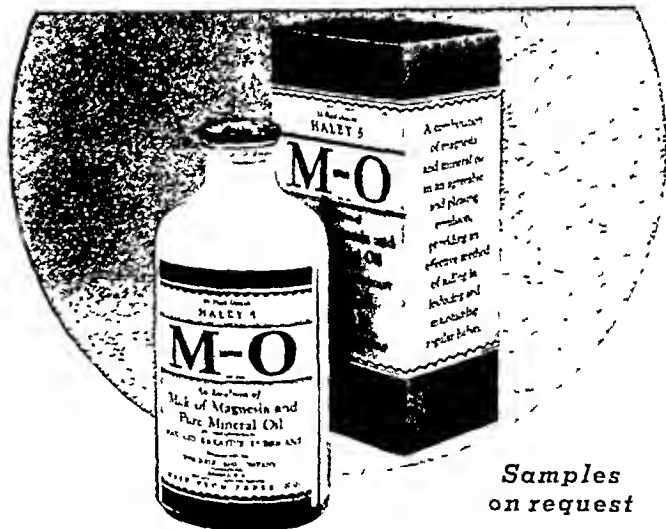
As far back as 1874, Carl Reuber demonstrated that certain definite changes occur in the synovial mem-

brane in immobilization of normal joints.

Gastrostomy was first suggested Eggebert, in 1837. Blandlot, in 18 performed this operation on a du In 1843, both Sedielat and Nelaton independently and successfully carried out this procedure in man. Only a few less than forty modifications of the original procedure has been offered.

Scoliosis is one of the oldest conditions described in medical literature. Hippocrates used this term to describe any twisted spine.

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William Turner, in 1886, wrote "with the exception of the skull no portion of the skeleton presents greater individual variations than the pelvis". Vesalius' drawing of the pelvis showed the sacrum to consist of six segments. Oddly, the writings of Deventer published in 1725, also describes the sacrum as consisting of six segments.

SPRAGUE, E. W., SCHAAF, R. A., MACARTHUR, C., HAWKES, S. Z., HAUTMAN, H., AND HALEY, P. W.

A Study of Appendicitis. S. G. O., Vol. 66, No. 2, pp. 166-172. Feb. 1, 1938.

The authors present a review of

1463 consecutive cases of acute appendicitis, all of which were operated upon. The technique was practically the same in all cases; the appendix being crushed, ligated, then severed with a cautery and inverted by means of a purse string suture. A row of Czerny-Lembert sutures is used to cover this and the raw edges of the meso-appendix. The appendix was not removed in three cases, which were complicated by general peritonitis. In septic cases great care is exercised to protect the healthy peritoneum. Abscesses are drained without entering the general peritoneal cavity if possible. The history of chills or the presence of a remittent type of fever

curve was taken to indicate the presence of the thrombophlebitis of some extent.

The authors have not used the so-called expectant treatment in any of these cases because they feel unable to judge which cases may localize safely and which ones may extend and continue to spread.

The conclusion is apparent from this study that operation is comparatively safe during the first 18 hours after onset. After that time the danger rises in direct proportion to the time elapsing between the onset and the time of operation. The mortality in this series of cases is 2.73 per cent.

Ten tables accompany the article.

Nelson M. Percy, Chicago.

GAUNT, WILLIAM E., IRVING, JAMES T. AND THOMPSON, WILLIAM.

Calcium and Phosphorus Deficiencies in a Poor Human Dietary. British Med. Jour., 770-773, April 9, 1938.

Experiments are cited in which it was shown that the nutritional value of a poor human dietary can be greatly improved by the addition of milk, and green food supplements. Experiments reported here demonstrate that in rats bred from stock this improvement is due largely to the calcium and phosphorus contained in the supplements. This conclusion is based upon a comparison of the rate of the growth, calcification of bones and teeth, and reproductive performance in various groups of rats, all bred from stock.

Hanes M. Fowler, Fort Wayne.

VAUGHAN, WARREN T.

Food Idiosyncrasy as a Factor of Importance in Gastro-enterology and in Allergy. The Review of Gastroenterology, March, 1938.

The first reference in all literature which might be taken as pertinent to the subject of food idiosyncrasy was the statement of Lucretius, a Roman—"One man's food may be highly poisonous to another," since corrupted into "One man's meat is another man's poison." Allergy and idiosyncrasy mean precisely the same thing today, although perhaps the term "sensitive" in connection with foods might be considered more general. Wolff-Eisner's suggestion in 1906 that hay fever might be an allergic disease first showed that there might be a connection between experimental anaphylaxis and spontaneous clinical disease, but it was not until 1910 that Doerr suggested a common basis for food idiosyncrasy and anaphylaxis. The first book on clinical allergy, by Minet and LeClercq in 1913, devoted only nine pages to food allergy and concluded that the phenomenon must be quite rare. Schloss in America in



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1912 applied skin tests and showed that, while explosive instances of food allergy were not common, that a wide variety of milder symptoms could be attributed to the same cause. Allergic symptoms referable to the digestive tract may result from food or drugs. The two commonest manifestations in the lips and mouth are angioneurotic edema and stomatitis following the ingestion of foods or drugs or the use of dental powders, pastes, mouth washes or even chewing gum. The recurrent form of herpes labialis is not infrequently associated with food allergy, and the same applies to many cases of recurrent canker sores in the

mouth. The classical allergic reaction in the stomach is associated with nausea and vomiting soon after the ingestion of the allergic excitant: if the latter is not vomited, the colon may later react with diarrhea and even true mucous colitis. Even perianal eczema may be due to food allergy and it seems that about one-third of cases of pruritis ani and perianal eczema, which are not due to pathologic conditions in the rectum can be relieved by a carefully studied plan of food avoidances. It is probably true that at times symptoms of gall bladder disease are due not to gall bladder infection but to the

effects on the gall bladder of food allergy, for it has been shown that in a sensitized animal, the local chemical irritation of a tissue may result in the accumulation of antigen at the point irritated; and it is recognized that the empirically-discovered gall bladder diets usually eliminated such definitely allergy-producing foods as strawberries and sea foods. Thus allergy may become a local complication superimposed upon the basis of an infected gall bladder. For the same reason, some cases of peptic ulcer have superimposed upon the ulcer a definite tendency to local allergic reaction, and in such cases the avoidance of the allergy-inducing food (notably milk) may result in symptomatic improvement very promptly. At times the symptoms of appendicitis may be imitated by food allergy. Some patients with characteristic history of chronic appendicitis, but who did not improve after operation, were found to have marked eosinophilic infiltration of their amputated appendices, and it was considered that this "appendiceal allergy" was but a part of an allergic colitis. The Walzer reaction suggested that possibly proteins are often absorbed from the digestive tract in a sufficiently unaltered state to be antigenic after absorption, but the further work of Thiers and Chevallier indicated that even after gastric digestion and after removal of protein by ultra-filtration food could still be allergy-producing. Possibly the active factor is not the protein but an associated hapten. The leukopenic index is more reliable than the skin tests in determining allergic substances in individual cases, but both ought to be used. The elimination diets of Rowe or the food diary of Vaughan are useful in detecting the offending food in many obscure cases. At the lowest estimate ten per cent of the population of the United States is frankly allergic, and for that reason it becomes evident that allergy must play a considerable part in the study of gastro-intestinal symptomatology.

LEVINE, A. L. AND SHUSHAN, MORRIS.
The Value of the Medical Plan of Treatment in Intestinal Obstruction. The Review of Gastro-enterology, March, 1938.

A middle position may be discovered between those who believe that intestinal obstruction is invariably a surgical emergency and those who do not, and careful study, undertaken for the purpose of creating distinctions may persuade medical nihilists that medical treatment has a definite place, not only because many cases ought to be operated upon only as a last resort but because medical treatment forms a vital pre- and post-operative requirement, none too well

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BASIC OPERATIONS IN COMMERCIAL CANNING PROCEDURES

VI. COOLING THE TIN CONTAINER AFTER THERMAL PROCESSING

● On this page we have previously described certain basic operations in commercial canning procedures. These have included cleansing of the raw material; blanching; exhausting or pre-heating; sealing the tin container; and thermal processing of the sealed container. In this—the last of this series—we shall discuss the final basic operation, namely, the cooling of the sealed can immediately after the heat process.

One main reason for rapid and thorough cooling of the can contents—as soon as the objective of the heat treatment has been fulfilled—is more or less self-evident. Prompt cooling checks the action of the heat and thus prevents undue softening in texture or change in color of the food. Also important, particularly in the case of foods of an acid nature, is the prevention of excessive chemical action between the food and the metal container, which may occur if the contents of the can remain hot for an extended period of time. In modern practice, two types of cooling are commonly used, namely, air cooling and water cooling.

Air cooling, as the name implies, involves cooling of the tin container by facilitating radiation of its heat into the air. This type of cooling is adaptable to certain products in small cans. In other products, or in the case of larger cans, it is employed chiefly when the slower loss of heat, characteristic of this cooling method, is essential either for preservation of the food, or for the production of certain quality characteristics in the final product. Modern air cooling is accomplished in well ventilated, specially designed warehouses where the cans are piled in rows, allowing ample space between rows for efficient air circulation.

The several methods of water cooling and the technique by which they are carried out are detailed elsewhere (1). Briefly, water cooling may be effected in a variety of ways. The hot cans may be cooled by admitting water into the retort in which they were processed, or they may be cooled after removal from the retort by conveying the cans through tanks of cold, running water or through cold water showers. Large size, or irregularly shaped cans—processed under steam pressure—must be cooled in the closed retort at the end of the process to avoid undue strain on the containers. This is accomplished by “pressure cooling” in which pressure is maintained in the retort during the cooling of the cans, to counterbalance the pressure which develops during the process within the can itself. Commercially, cans are water-cooled to about 100°F. so that enough residual heat remains to dry the can exterior.

Present day canners are fully aware of the importance of cooling their products rapidly and completely as soon as the process is completed, in order to insure the production of canned foods with high quality characteristics. Consequently, in modern canneries the cooling operations are strictly supervised like the other basic operations in the commercial canning procedure. After inspection and labeling, the cooled cans are then ready to enter distribution channels for delivery to the consumer.

In this series of six discussions, we have attempted not only to describe the basic steps in commercial canning procedures, but also to explain their purposes. We trust this series may help bring a better understanding of this important method of food preservation.

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(1) 1936. A Complete Course in Canning, 6th Ed. The Canning Trade, Baltimore.

This is the thirty-ninth in a series of monthly articles, which summarize, for your convenience, the conclusions about canned foods reached by authorities in nutritional research. We want to make this series valuable to you, so we ask your help. Will you tell us on a post card addressed to the American Can Company, New York, N. Y., what phases of canned foods knowledge are of greatest interest to you? Your suggestions will determine the subject matter of future articles.

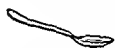


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recognized at the present time. Since obstruction is at times due to fecoliths and encrusted gall stones attempting passage through the bowel, operation ought to be delayed until the colon can be flushed out and the stomach and duodenum drained by catheter in a double effort to relieve obstruction and intoxication, because so frequently operation results in death from surgical shock even though the cause of the obstruction be very simple. Whether the cause be obstruction, paralysis or reflex ileus, the symptoms depend largely on the position of the block, high blockage being the most dangerous and rapid in development, and resulting in a quick dehydration and chloride deprivation. Frequent lavage of the stomach via the nasal catheter, the introduction of fluids and dilute HCl through this catheter at intervals, oil enemas, interstitial injection of 2,000 cc. of glucose in saline each 24 hours, the heat tent over the abdomen, cardiac stimulants and morphine for rest are suggested, both pre-operatively and postoperatively. Complete cooperation between surgeon and gastro-enterologist spells a high measure of success.

DE RIVAS, DAMASO.

The Rational Treatment of Amebic Dysentery with Special Reference to the Eradication of the Parasite by the Intra-colonic Thermic Method. The Review of Gastro-enterology, March, 1938.

The author uses colonic instillations of a 1-5000 copper sulphate in saline solution with glycerine and laudanum added, keeping the temperature very close to 45 to 47 degrees C. It is a procedure which is non-effective or even dangerous in inexperienced hands and depends for its efficacy upon the critical death point of *Endameba histolytica*. He relies upon the sufficiently frequent use of this method more securely than upon the use of any drug, and checks the progress by the presence of amebae or cysts or occult blood in the stools. and the healing of the ulcers, but not by the presence or absence of symptoms. He quotes Smithies as support in the idea of ceasing to rely upon many expensive drugs with claimed specificity of action, and compares Amebiasis to syphilis, in that both diseases are more efficiently cured by prolonged careful application of simple and known remedies than by the erratic use of new and much vaunted ones.

HARTZELL, J. B.

The Treatment of Fistulas of the Small Intestine. S. G. O., Vol. 66, No. 1, pp. 103-116, Jan., 1938.

The author discusses the treatment of small fistulas by means of pastes, buttons, discs and other devices and presents his modification of the rubber

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disc. The efferent and afferent limbs of the fistula are probed and a wax model of the interior of the bowel is made. This is long enough to extend well into healthy bowel. This model is then cast in pliable rubber, which is inserted into the limbs of the fistula. Into the exposed portion of this rubber mold a heavy silk suture is placed. If necessary two sutures are inserted at different points in the mold and fastened to a crossbar on the surface of the abdomen. As the fistula heals a smaller rubber mold is made and inserted. Finally after the fistula is completely healed the sutures may be cut and removed and the mold will pass through the intestinal tract.

Prerequisite to the success of this method is the complete absence of any degree of intestinal obstruction below the fistulous opening.

Eighteen figures from case reports and a bibliography accompany the article.

Nelson M. Percy, Chicago.

HAWKES, STUART Z.

Thrombophlebitis of the Appendiceal Vein Complicating Acute Appendicitis. S. G. O., Vol. 66, No. 1, pp. 62-78, Jan., 1938.

Thrombophlebitis of the appendiceal vein occurs when the infection tends to spread through the tissues. This thrombus serves to stop the spread of infection, but if the infection is so virulent as to cause enlargement of the thrombus and extension of it proximally in the appendiceal vein small emboli may break off and lodge in the liver. Such a happening is usually denoted by the occurrence of a chill and a sharp rise in the patient's temperature. This is frequently the beginning of a liver abscess and marks that case of appendicitis as one with a more grave outlook. If the thrombus has extended beyond the appendiceal vein and is giving off small emboli from a point in the ileo-colic vein it should be excised or ligated at the time the appendix is removed. If simple appendectomy without excision or ligation of the thrombosed vein is performed the patient will continue to have chills post-operatively and the possibility of the development of a liver abscess becomes much greater.

The author describes the course of the appendiceal and the ileo-colic vein and points out that the ligature should be placed at a point distal to the juncture of that vein with the right colic vein.

Early recognition and proper treatment of this type of appendicitis the author believes may contribute to lowering the mortality rate of appendicitis as a whole.

Three figures and a summary of eight cases accompany the article.

Nelson M. Percy, Chicago.

BERMAN, J. K.

Congenital Anomalies of the Rectum and Anus. S. G. O., Vol. 66, No. 1, pp. 11-22, Jan., 1938.

Congenital anomalies of the rectum and anus are rare. Their diagnosis presents no difficulty but recognition of the type of anomaly present requires a complete knowledge of the embryological development of the mesenteron and proctodeum.

Anomalies of the anus arise from maldevelopment of the proctodeum, while those of the rectum result from maldevelopment of the mesenteron. An accurate anatomical classification as proposed by Fraser, follows:

1. Congenital narrowing of the anal canal.
2. Congenital occlusion of the anal canal.
3. Abnormal location of the anus.
4. Congenital absence of the anus.
5. Total absence of the rectum.
6. Atresia of the lower end of the rectum.
7. Membranous occlusion of the rectum.
8. Recto-vaginal, recto-urethral and recto-vesical fistulas.

The symptoms are those of complete or partial intestinal obstruction with distension of the abdomen. In the fistulous types the parents will have noted that there is an abnormal opening with an absence of the normal anus.

The diagnosis is difficult. X-ray examinations with the baby held in an upside down position will reveal the position of the blind gut if it contains gas. Gas is rarely present beyond the hepatic flexure during the first 24 hours of life. Fluoroscopy with massage of gas into the blind gut is a valuable method. Injections of 12½ per cent sodium Iodide into an external fistula will reveal the course of an internal fistula if one is present. Colostomy and digital exploration of the blind gut is dangerous.

Treatment depends on the type of anomaly present and the accuracy of diagnosis. Colostomy should be avoided if possible. Dissections should be made from below through a longitudinal incision from the perineal body to the tip of the coccyx. This will be through the sphincter muscle which develops independently in the regional mesenchyma. Local anesthesia should be used as the straining and crying of the baby tends to push the blind gut down in the desired position. If a fistula is present it should be left alone until the child is older. The author uses No. 0 catgut to suture the mucosa of the bowel to the skin.

A brief summary of 23 cases of congenital anomaly of the rectum and anus with eleven figures and two tables accompany the article.

Nelson M. Percy, Chicago.

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MULHOLLAND, H. B.

Intravenous Liver Extract in the Therapy of Pernicious Anemia: Report of a Case. Ann. Int. Med., Vol. 11, No. 4, p. 671, Oct., 1937.

The author states that some cases of pernicious anemia will not respond to liver or liver extract and ventriculin when given orally but will respond to intramuscular injections of liver extract. The author cites a very comprehensive case history, over a period of eighteen months, in which oral administration of liver extract was efficient for a period, then failed; intramuscular injections reacted similarly and was then followed by five intravenous injections of 20 c.c. of specially prepared liver extract, with less reaction to each successive dose and causing such improvement that the patient was able to leave the hospital for his home. Since then he has used one intramuscular injection of liver extract each week. Over a stay of 120 days in the hospital both the blood picture and general health were much improved.

In his comments Dr. Mulholland reviews the literature of other authors in which liver extract was administered intravenously.

B. E. Vincent Lyon and C. H. Aronld.

VAUGHAN, JANET M.

Anemia and the Gastro-intestinal Tract. British Med. Jour., 57-59, July 9, 1938.

It is recognized today that the commonest cause of anemia is a lack of one or other of the essential hemopoietic principles. The known hemopoietic principles are iron, the P.A. substance in liver effective in Addisonian pernicious anemia, and vitamin C. Minute quantities of such minerals as copper, cobalt, and manganese may be

required but are usually present in adequate amounts even in the poorest diets.

An adequate supply of hemopoietic principles may be rendered inadequate due to certain disturbances of the gastro-intestinal tract such as, hemorrhage, deficiency of gastric digestion, deficiency of intestinal absorption, and production of toxic substances.

The commonest sources of gastro-intestinal hemorrhage are bleeding gastric and duodenal ulcers and hemorrhoids. In all cases of anemia of unknown etiology an analysis of the stools for occult blood is an essential investigation.

Deficiency of gastric digestion may be due to organic lesions, diminished secretion of hydrochloric acid, or diminished secretion of the intrinsic factor of Castle.

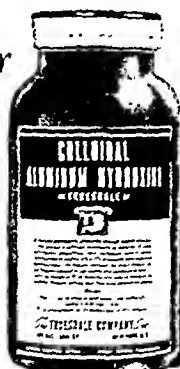
By organic lesions of the stomach are meant new growths and complete or partial gastric resection. The anemia in such cases is due in part to the diminished gastric secretion and in part to altered intestinal function. It usually responds well to treatment with iron and liver extract.

There is a high incidence of achlorhydria associated with all types of anemia, but the exact etiological relationship of gastric acid secretion to anemia has not been established because of conflicting evidence in the literature.

Some cases of Addisonian pernicious anemia also show an iron deficiency. In such cases large doses of iron must be given along with the liver extract to secure a satisfactory hemotological response. This point should be remembered in order to combat the onset or further development of subacute combined degeneration of the cord.

Deficiency of intestinal absorption may be due to changes in pH, increased motility, abnormalities of muscle tone, or abnormalities of the mucosa. The anemia seen in such conditions is often of a mixed type—that is, there is a deficiency of both the iron and the P.A. principle.

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Recent experimental work has shown that the production of toxic substances in the intestine associated with a deficiency of certain food substances in the diet may cause anemia, possibly of the hemolytic type. Such observations serve to emphasize the extraordinary importance of an adequate diet in maintaining normal health, and are a yet further indication of the close relationship of normal gastro-intestinal function to normal hemopoiesis.

Hanes Fowler, Fort Wayne.

ANNUAL MEETING OF AMERICAN CONGRESS OF PHYSICAL THERAPY

The 17th annual scientific and clinical session of the American Congress of Physical Therapy will be held co-operatively with the 22nd annual convention of the American Occupational Therapy Association, September 12, 13, 14 and 15, 1938, at the Palmer House, Chicago. Preceding these sessions, the Congress will conduct an intensive instruction seminar in physical therapy for physicians and technicians—September 7, 8, 9 and 10.

The convention proper will have numerous special program features, a variety of papers and addresses, clinical conferences, round table talks, and extensive scientific and technical exhibits.

The instruction seminar should prove of unusual interest to everyone interested in the fundamentals and in the newer advances in physical therapy. The faculty will be comprised of experienced teachers and clinicians; every subject in the physical therapy field will be covered. Information concerning the convention and the instruction seminar may be obtained by addressing: The American Congress of Physical Therapy, 30 North Michigan Avenue, Chicago.

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Vitamins in Relation to Gastro-Intestinal Diseases*

By

MARTIN G. VORHAUS, M.D.
NEW YORK, NEW YORK

THE interest of the general practitioner in vitamins is growing rapidly. A few years ago the prevailing medical attitude was one of cynical ignorance. Today, stimulated by a large and increasing scientific literature, spurred on by the high pressure salesmanship of pharmaceutical firms and acutely aware of the general public curiosity aroused by the daily press and magazine articles, the doctor is in danger of becoming over-enthusiastic in his haste to jump on the "vitamin band-wagon".

It is admitted that cases of beriberi, pellagra, sprue and other deficiency states do exist, even in our own communities, with somewhat greater frequency than has been believed. These cases can and should be recognized earlier and treated properly. But the vitamin problem of today is much more than the recognition of the most advanced stage of vitamin lack. There is a larger number of patients who are suffering from a mild or moderate vitamin deficiency. These are the cases that are most important to recognize and treat.

How shall we recognize the pre-clinical stages of vitamin deficiencies?

Why does avitaminosis become of special interest to a gastro-intestinal symposium?

These two questions form the basis of this discussion but it is necessary to answer them in the reverse order.

Since the vitamin content of the diet is the basis of our normal intake, it becomes important at the onset to discuss foods and the factors which influence the digestion, absorption and utilization of these food factors.

A state of vitamin deficiency—either clinical or pre-clinical—may develop under the following conditions:

1. When there is an inadequate amount of vitamins in the diet.
2. With an adequate amount of vitamins in the diet when there is, A. An increased need for vitamins. B. A diminished absorption of vitamins. C. An increased destruction of vitamins. D. A diminished utilization of vitamins.

A poor vitamin intake frequently exists for a long time before it can be recognized clinically. A variety of causes results in a diminished intake and can be classified as follows:

I. Errors in Eating.

1. Malnutrition due to economic factors.
2. Malnutrition due to dietary ignorance.

A. Fads in diet—such as weight reduction diets. B. Eccentricities in diet—such as excess of carbohydrates. C. Chronic alcoholism—replacing part of the diet. D. Self imposed diets for the relief of symptoms, such as anorexia, dyspepsia or dysphagia. E. Prolonged adherence to diets prescribed by physicians especially in the treatment of: Peptic ulcer, chronic

nephritis, chronic colitis, allergic states, biliary tract disease, cardiac diseases.

IIA. Even when the vitamin content of the diet is adequate, there are many exigencies which may develop and as a result the need for one or more of the vitamins is increased. If a greater supply is not furnished, either by the diet or by additions thereto, a state of clinical or pre-clinical avitaminosis may ensue.

An increased need for vitamins occurs in:

1. Growth.
2. Pregnancy and lactation.
3. Increased work.
4. Increased metabolism (hyperthyroidism).
5. Infectious and toxic states and their convalescence.

IIB. Although a given diet may contain adequate amounts of all vitamins, there are many factors which interfere with the absorption of these vitamins. These may be classified as follows:

A diminished absorption of vitamins occurs with:

1. Vomiting.
2. Diarrhea.
3. Alteration of the gastro-intestinal mucosa due to a. Atrophy. b. Inflammation. c. Circulatory disturbances.
4. Alteration of the gastro-intestinal secretions, namely a. Gastric. b. Biliary. c. Pancreatic. d. Intestinal.
5. Alteration of gastro-intestinal continuity by a. Surgery (short-circuiting operations). b. Internal fistulae—such as gastro-colic, etc. e. External fistulae—biliary, pancreatic, etc.

IIC. It is well known that certain vitamins are easily destroyed in the body and that although the diet is adequate in this respect, a state of deficiency may develop.

Increased destruction of vitamin may occur with: 1. Diminished or absent gastro-intestinal secretions. 2. Bacterial and chemical interactions.

IID. Finally, while the diet may be adequate and the factors of need, absorption and destruction have all been taken into account, there still remains the possibility that the cells of the body may not be able to utilize certain vitamins either in part or in toto.

Diminished utilization of vitamins may occur with:

1. Achylia.
2. Gastric resections—especially subtotal.
3. Advanced hepatic disease.
4. Advanced pancreatic disease.
5. Advanced renal disease (?).

It has not been proven that renal disease interferes with vitamin utilization but there is suggestive evidence in this respect, especially in relation to the nephrotic types of chronic renal disease.

This schematic representation of factors favoring vitamin deficiency conclusively demonstrates an intimate inter-relationship to gastro-intestinal disorders.

Once we are aware of this association, it becomes our responsibility to be on the lookout not only for the outspoken clinical syndromes of advanced avitaminosis but to recognize or at least suspect—the milder or pre-clinical deficiency states. With this in mind it is desirable to review some of the knowledge derived from animal experiments and to emphasize those factors which are particularly germane to our human problems.

*Read before the Gastro-Intestinal Department, Beth-El Hospital, Brooklyn, N. Y., February 21, 1938.
Submitted February 25, 1938.

When an animal is deprived entirely of a single vitamin, a disease state develops which is characteristic. The rate at which this experimental deficiency develops varies with different species as well as within members of the same species. It is modified by the preceding health of the animal as well as by the degree of storage of that and other vitamins in the body of the animal prior to the experiment. It is further influenced by the need of that animal for the vitamin in question—a need which is dependent upon growth, pregnancy, work, temperature and many other factors.

In spite of all these variables—known and unknown the complete absence of one vitamin in the diet of an animal is followed by a well recognized disease state. However, when an animal is given a diet deficient in one vitamin but in which that vitamin is not entirely absent, the observations of such an animal's state of health are less clear cut. In some instances a fairly well recognized pathologic state is observed yet often the experimental results vary considerably. Some animals may appear to remain well while others develop a group of bizarre signs which are difficult to explain or classify.

As an illustration of this point, Cowgill (6) points out that when dogs are kept on a diet markedly deficient in riboflavin (vitamin G), they develop a profound collapse in about four months. At this time if they are given riboflavin by parenteral injection, the dogs recover quickly. In six hours they are able to stand again and in twenty hours they can run around and appear to be normal. However, if dogs are kept on a diet which is less deficient in riboflavin (i. e. given one-half of the daily requirement of this vitamin) they do not develop the characteristic collapse. These dogs live eight months or longer and finally develop an ataxia with pathologic changes in the spinal cord.

This illustration by Cowgill is not an exceptional one. It has been repeated by many experimentors with the other vitamins in many different species. It is thus apparent that there is a considerable difference in the pathologic states of animals in which a single vitamin is completely withheld or in which a fraction of the daily requirement of that one vitamin is given.

In reviewing those animal experiments in which several vitamins are partially deficient in the diet, the differences in the observations of these animals become more marked and more confusing. Yet it is most frequently the case that the patient who seeks help is more likely to be partially deficient in several vitamins rather than to lack only one.

Clinical counterparts of these animal experiments are being recognized. Recently the photometer has demonstrated that the physician does not need to wait for xerophthalmia to diagnose a vitamin A deficiency. Even the symptom of night blindness may not be present. Recent photometric tests have shown a partial deficiency of vitamin A in 50% of a group of adult ambulatory out-patients (5).

Unfortunately there has not yet been developed a similar simple method for the determination of sub-clinical stages of the other vitamin deficiencies. But the lessons of animal experimentation teach us not to look only for the well developed picture of acute or complete avitaminosis such as beriberi or scurvy. It is exceptional for man to exist under conditions of complete or almost complete absence of any one vitamin. The much more frequent clinical state is one of

mild or partial deficiency of one or several vitamins over a long period of time.

At present the published clinical papers seem to be more concerned with case reports of instances of advanced vitamin deficiency occurring in some other disease. An illustrative collection of such case reports is tabulated.

VITAMIN A DEFICIENCY

With extensive hepatic disease—Blegvad (2).

With gastro-colic fistula—Wilbur and Snell (19).

With congenital atresia of bile ducts—Altschule (1).

VITAMIN B DEFICIENCY—THIAMIN

With side tracking of most of small intestines—Urmey et al. (18).

With post operative ileal stricture—Jones (11).

With ulcerative colitis and hyperthyroidism—Jones (11).

With jaundice due to stones in common duct—McVicar (14).

VITAMIN C DEFICIENCY—ASCORBIC ACID

With prolonged use of diet for duodenal ulcer—Jones (11).

With prolonged use of diet for ulcerative colitis—Jones (11).

With chronic jaundice—Many authors (9, 12, 17).

VITAMIN G DEFICIENCY—RIBOFLAVIN

With diffuse gastro-enteritis—Wilbur and Snell (19).

With rectal diarrhea—Boggs and Podget (3).

SPRUE

With extensive atrophy of intestinal mucosa—Snell (16).

With carcinoma or atrophy of pancreas—Snell (16).

With gastro-colic fistula—Snell (16).

With tuberculosis of lymph nodes—Snell (16).

With prolonged diet after resection for carcinoma of tongue—Jones (11).

These case reports are the counterpart of animal experiments especially where complete or almost complete absence of one vitamin has been instituted. In addition to animal observations, further information regarding vitamins has been procured by another method—namely that of feeding large amounts of vitamins to human subjects. In this manner Jolliffe (10, 7) and his co-workers have conclusively proven that alcoholic polyneuritis is not due to alcohol but is a vitamin deficiency due to lack of thiamin (vitamin B). Similarly Carroll (4) has demonstrated that in tobacco-alcohol amblyopia the addition of multiple vitamins to the diet results in a large percentage of marked improvement even though the use of tobacco and alcohol is continued.

MacKie (13) reports an interesting group of cases of ulcerative colitis in which 62.6% had symptoms which could be interpreted as evidence of deficiency states.

Similar reports (8) are being published which increase our awareness of the frequency with which mild deficiency states may be associated with gastro-intestinal diseases. With this in mind, it becomes important to recheck constantly the vitamin content of

those patients' diets who require long continued food restrictions.

Vitamin A rich foods are: spinach, escarole, greens, carrots, butter, eggs, cream and liver. If these foods must be restricted in the diet, the necessary vitamin A can easily be replaced by one of the many fish liver oil preparations.

The daily adult requirement of vitamin A is about 5000 international units.

Vitamin B—Thiamin is the one vitamin most likely to be deficient in the average diet. It is present in fairly good amounts in relatively few food stuffs. In addition Thiamin is heat labile and water soluble. Cooking destroys some of this vitamin but under usual conditions only a small amount is lost this way. A larger amount of this vitamin is wasted by discarding the water in which foods are cooked.

Coarse grains contain a large amount of Thiamin especially wheat germ. Whole wheat has more than six times the amount of this vitamin than is found in white flour, while wheat germ is almost fifty times richer than flour.

Milk and eggs contain good amounts of Thiamin but it is well to keep in mind that if the patient depends upon these foods alone for this vitamin, he must ingest over two quarts of milk or forty eggs daily to insure minimal requirements. Among the meats the largest Thiamin content is in lean pork and in beef liver. Interestingly enough, lean pork has seven times more of this vitamin than beef. Other foods with a fair amount of Thiamin are kidney beans, peanuts, dried peas, brown rice and crude cane molasses.

The daily adult requirement of Thiamin is from 1 to 2 mgms. but usually up to 4 mgms. may be needed in health.

Vitamin C—Ascorbic Acid is derived mainly from citrus fruits, also spinach, peppers, turnips, greens and parsley.

It is also water soluble and heat labile.

The daily adult requirement of Ascorbic Acid is from 40 to 60 mgms.

Vitamin D is not included in our consideration since it appears to have no relationship to gastro-intestinal disorders.

Vitamin G—Riboflavin is derived mainly from liver, kidney, milk, eggs, prunes, wheat germ and tangerines. Yeast is also a very good source of this vitamin.

The daily adult requirement has not yet been adequately determined.

After having checked the diet of a patient, the physician must depend upon his clinical judgement for the diagnosis of milder deficiency states. One important aid in the diagnosis is the tongue. A careful examination of the tongue often offers the first clue. The red tongue of sprue, the bald tongue of macrocytic anemias, the swollen tongue so often but not constantly encountered in pellagra are early signs and can be recognized often before other clinical symptoms and signs are available. Careful scrutiny of the mouth will show at times early signs of gingivitis or beginning bleeding which should arouse the suspicion of a vitamin C deficiency.

The presence of a persistent diarrhea—even though mild—might be the first symptom of early pellagra and its presence should encourage the physician to look for early skin lesions, especially on the backs of the hands and on the face and neck.

Unexplained loss of appetite is occasionally the first

symptom of a B deficiency but unfortunately anorexia is also the first symptom of many slowly developing organic or psychic disorders. Vague but persistent pains in the legs, recurrent attacks of back pain or stiff neck in an obese individual warrant a clinical suspicion of vitamin B deficiency.

And finally the laboratory may add some suggestive information towards the solution of these clinical problems. Unexplained anemias, especially of the macrocytic type—even though mild—should receive careful consideration from the clinician, and the X-ray finding of osteoporosis in a young or middle-aged individual may well be an early indication of avitaminosis.

In addition it is well to remember a note of warning from those workers in the animal field who remind us that the members of a species larger in weight or height than the average, have a proportionally greater vitamin requirement.

A great deal of attention is directed repeatedly to the increased vitamin needs during growth and pregnancy but not enough stress has been laid upon the equally increased vitamin requirements of patients with hyperthyroidism, cirrhosis of the liver, diabetes, gout and chronic osteoarthritis, as well as the needs of the normal man or woman who is constantly overworking—either physically or mentally.

There is one more point to discuss before closing, and that is the relationship of vitamin lack to pre-operative preparation of the patient. It has been axiomatic in our better hospitals for the surgeon to invite the co-operation of the internist in preparing many patients for operation. This is particularly true in cases of diabetes and cardiac disease. Recently Means (15) has stressed this need in the pre-operative preparation of thyroid patients. In this respect the use of iodine is only one factor but of equal importance is the replenishing of the vitamin lack. Means has shown a decided drop in mortality from surgery after instituting this regime.

Too few surgeons have this point of view in regard to severe gastro-intestinal diseases. Repeatedly operations are performed in the presence of chronic diseases associated with deficiency states with no other pre-operative preparation than a transfusion. This is true especially in cases of chronic peptic ulcer, slowly developing gastro-intestinal carcinoma and chronic biliary tract disease with low grade infection and liver involvement. Extensive intestinal surgery is performed upon patients with chronic regional ileocolitis with little or no thought of bringing the vitamin lack up to normal.

As surgeons become more aware that vitamin deficiency states have a very important prognostic significance, the internist will be given more opportunities to adequately prepare a patient for operation. With a reduction in operative mortality in all hospitals—as has been the case in a few already—the use of the term "shock" as the cause of death will show a marked decline.

CONCLUSION

A state of ill health is often the result of a faulty diet but even in the presence of a normal diet, deficiency states may develop. The awareness of avitaminosis will often direct the internist to recognize the outspoken clinical states and to suspect the pre-clinical stages of vitamin deficiencies.

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Studies on the Parallel Action of Vitamin C and Calcium

By

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NEW YORK, NEW YORK

THE synthesis of cevitamic acid has made possible not only further physiologic study of Vitamin C action but also its chemical role. In a general way the relationship of action between Vitamin C and calcium has been assumed. It is, therefore, significant to point out the direct chemical relationship between the two.

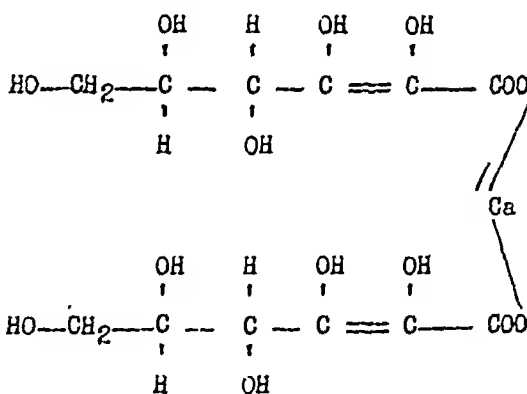
Calcium, forming the architectonic tissue of the body, is essentially a highly insoluble ion at biologic Ph ranges. As the carbonate, it is one of the most insoluble of substances. Its solubility is somewhat influenced by CO_2 , by parathyroid hormone and the hydrochloric acid of the stomach. In the absorption of calcium from the small intestine, none of these factors are present. It was, therefore, essential to find some other agent possessing solubilizing properties for calcium.

In the course of my chemical studies on Vitamin C, I was surprised to find that Vitamin C could dissolve the insoluble calcium carbonate with a rapidity and completeness second only to fairly strong hydrochloric acid. For a biologic acid this action was unique and quite unexpected since gluconic acid which is a sugar quite similar in structure but differing in the double bond and two hydrogen atoms, forms a solution of calcium only to 3% as the calcium gluconate. By special stabilizing procedure, supersaturated solutions up to 10% are formed and through the glucono gluconate 20% solutions are attained. It was, therefore, striking to find that cevitamic acid formed 100% solutions of calcium and in fact was hygroscopic. This marked solubility suggested the possibility of a strong ionizing influence on calcium and a series of experiments were carried out with the following results. As a basis of comparison the most soluble injectable salts were taken, that is, the calcium gluconate and calcium galactate gluconate.

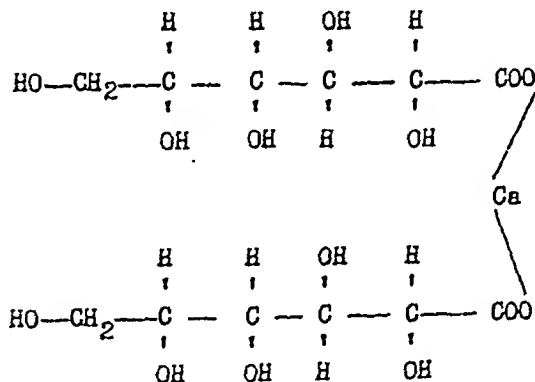
The formula of Calcium Cevitamate, and its close relationship to gluconate, is graphically demonstrated in the accompanying illustration. One notes that there is a difference of two hydrogen atoms, and the pres-

ence of a double bond in the cevitamate giving it the oxidation reduction properties.

Calcium Cevitamate



Calcium Gluconate



It is a yellowish white amorphous powder manifesting a ready solubility, making it available in physiologic solutions up to (40%). It is non-irritating on injection, either subcutaneously, intramuscularly or intravenously, and is well tolerated by the gastro-intestinal tract.

In view of the marked solubility of Calcium Cevitamate, a difference in ionization of the two salts suggested itself and the following experiments were performed and the results recorded.

A comparison of the ionization of the two salts is as follows:

Salt	% Solution by Weight	Concentration Moles/Liter	Temperature Drop °C.	% Ionization	Yield Ca ion Per Gram Salt	Yield Ca ion Per cc. Solution
Calcium Cevitamate	5%	.123	.577	74.6	.0700	.0037
"	10%	.261	1.085	60.0	.0563	.0063
"	20%	.589	2.362	58.1	.0546	.0137
"	30%	1.008	3.940	55.3	.0528	.0226
Neo-Gluconate	10%	.125	.565	*47.8	.0323	.0048
"	20%	.273	1.120	*40.3	.0273	.0088
Calgluconate	3%	.072	.263	48.6	.0452	.0014

*Since the structure of the Neo-Calgluconate is not known, and since its empirical formula is $(C_{26}H_{44}O_{28}) Ca_2$, we have assumed that it ionizes as follows: $Ca_2C_{26}H_{44}O_{28} \longrightarrow 2 Ca \quad 2(C_{13}H_{22}O_{14})$

An analysis of these findings would tend to indicate that the Calcium Cevitamate in 5% solution was approximately equivalent to the neo-gluconate in 10% solution and that the 10% Calcium Cevitamate was approximately equivalent to the 20% neo-gluconate.

The comparative series was run only to 30% Calcium Cevitamate because the neo-gluconate solutions do not exceed 20%. In considering the calglucon tablet which is only 3% soluble the yield of calcium ions per cc. of solution was .0014 whereas that of the Calcium Cevitamate in only 30% solution was .0226 or about twenty times greater. If calculated on the basis of 100% it would be in the vicinity of sixty times greater in calcium ion content per cc. solution. How important this factor can be in the question of calcium absorbability becomes apparent from the volume of solute necessary to obtain an equal amount of available calcium. For every 100 cc. of solute required for the absorption of Calcium Cevitamate it would require 6000 cc. of solute for an equal availability of calcium in gluconate. Since the total fluid content of the gastro-intestinal canal is about 5000 cc. and absorption of calcium occurs only in the upper intestine, the difference in absorbability between Calcium Cevitamate and calcium gluconate becomes apparent.

The action of cevitic acid on the ionization of calcium opens up a field both of theory and practice. A comparison of the physiologic action of cevitic acid and calcium shows an almost completely parallel action in bone metabolism, hemorrhagic diathesis, cell membrane permeability and detoxicating action. So close is this resemblance that one can interchange their functions. It is this element which suggests that cevitic acid may be the factor which acts as the vehicle for the diffusible fraction of the serum calcium. There is a strong probability that the parathyroid hormone and cevitic acid jointly balance the small fraction of

ionized diffusible calcium. Greenwald is quoted by Cantarow as suggesting that some of the calcium is bound to an organic substance in a citric like combination, the compound being intimately connected with the parathyroid hormone probably diffusible and slightly ionized. Belief in the existence of such a compound is also shared by Klinke and by Dendroy and Hastings. The latter drew attention to the similarity of action of the parathyroid hormone and citrate solutions in holding calcium in solution. In view of the fact that calcium citrate is only .8% soluble it is difficult to conceive of citrate as a calcium solubilizing

agent. Cevitic acid, however, has precisely the desired action on the ionization of calcium and its distribution in the intestinal canal, pituitary and adrenal makes it a much better hypothetical agent than citrate.

From the practical aspect it is important to note that the injection of Calcium Cevitamate is non-irritating and better tolerated than gluconate.

We may summarize the parallel action of calcium and vitamin C as follows:

1. Alter cell permeability.
2. Inhibit, exudates and transudates.
3. Decrease nerve irritability.
4. Increase coagulability of blood.
5. Inhibit allergic reactions.
6. Possesses a detoxicating action on heavy metals, and arsenic.
7. Participates in tooth and bone growth.

Thus, Borbely has shown that after a calcium injection it takes a much longer time and stronger suction to produce intradermal hemorrhage in an area of skin covered by a suction cup. Gothlin (?) used the same test for determining Vitamin C deficiency clinically.

In describing capillary hemorrhages, as the consequences of vascular congestion in the course of chronic infections, and the cause of hemorrhagic symptoms in acute infectious diseases, Kugelmass (4) has recommended the use of Calcium. On the other hand, Lundeidei (5) showed that large doses of ascorbic acid have a favorable influence in hemorrhagic conditions. Lamin (6) demonstrated that bleeding time in rabbits was decreased 17-22% less than an hour after the injection.

A remarkable similarity in physiologic action exists between calcium and Vitamin C in various diseases which I will describe briefly. Their actions in allergy are so alike as to make Calcium Cevitamate a double acting agent with the same physiologic re-

sponse and, at the same time, securing an intensification of calcium action hitherto unobtainable in similar dosage. To indicate the variety of applications, we find that in the treatment of purpura hemorrhagica for which calcium is commonly used, A. Sa and O. A. Prestera (8) attributed the recovery to a subsidence of Vitamin C deficiency. In tooth and bone growth, where calcium plays a dominant role, Vitamin C has been demonstrated to be a vital partner without which normal calcium metabolism could not be maintained as shown by A. A. Mikhailova (9).

The diuretic action of calcium, in acute and chronic nephritis, nephrosis and ascites, is also possessed by Vitamin C as described by M. A. Abbasy (10). He showed under carefully controlled conditions, that Vitamin C possessed a specific diuretic effect on human beings. Another physiologic action common to both Vitamin C and calcium is their effect on the vegetative nervous system. Calcium diminishes neuromuscular irritability, and vasomotor instability. Tislowitz (11) demonstrated in dogs that the injection of large doses of ascorbic acid caused a slowing of the heart beat, a decrease of 0.5° - 1.0° in body temperature, and a 10% increase in the alkali reserve. Conversely, it was shown by Sankaren and Krioluman (12) that guinea pigs on a diet, deficient in Vitamin C, developed tachycardia.

Again in tuberculosis, especially of the intestinal type, calcium has been favorably employed in reducing the diarrhea, and causing improvement of the local condition. Here too Vitamin C plays a similar role and has been claimed by Heinemann (13) to protect guinea pigs infected with tubercle bacilli against intestinal tuberculosis. Likewise, Petter (14) describes definite improvement in tuberculosis patients following administration of Vitamin C.

In adult rabbits, sensitized to horse serum, anaphylactic shock was entirely prevented, or its severity greatly decreased by the intravenous injection of 100 mg. cevitamic acid given 1-5 minutes before the shock injection. A. Hochwald (15) also showed that cevitamic acid in large amounts injected intravenously was therapeutic in hyper-sensitive states in human beings, and inhibits histamine shock. It has also been shown that diphtheria toxin and benzene poisoning are neutralized by Vitamin C; similarly, arsphenamine intoxication is combated by both cevitamic acid and calcium as shown by Otto Klin (16) and A. Meyer (17). F. Widenbaur and S. Saretz (18) describes the antitoxic activity of Vitamin C on Diphtheria toxin in man. Marion B. Sulzberger and Bernard L. Oser (19) showed the influence of Ascorbic Acid in Diet on Sensitization of Guinea Pigs to Neoarsphenamines. Important in this detoxicating mechanism are the oxidation reduction properties possessed by cevitamic acid through the action of the double bond. Thus, Klodt (20) suggests that the oxidized ascorbic acid, under low tension gives up its O to the hemoglobin-oxhemoglobin. Holtz (21) also speaks of ascorbic acid as an oxidation catalyst for unsaturated fat acids. How important this factor is in calcium metabolism becomes apparent from Cantarow's statement that "Disturbances of fat absorption act in impairing calcium absorption since the presence of large amounts of fatty acids in the intestine results in the formation of calcium soaps which being insoluble, are not absorbed and are eliminated in the feces." This disturbance has received too little at-

tention from those advocating large doses of calcium gluconate by mouth.

All of the above properties are possessed as well by calcium as by Vitamin C in striking parallel action.

Jungeblut (22) has also suggested the use of cevitamic acid in the prophylaxis of poliomyelitis because of its apparent virucidal action.

Another important relationship worth emphasizing, is that which exists between the adrenalin mechanism and Vitamin C. Cislighi (23) demonstrated certain similarities of the effects of 1-ascorbic acid, and adrenalin leading him to suggest that the vitamin stimulates adrenalin secretion. The role of ascorbic acid in oxidative processes is discussed. R. Tislowi (24) further showed that ascorbic acid caused a decreased blood volume, slight diuresis, a slight drop in the body temperature, increased vascular tonus, and has a vagotonic action on the circulation. He considers that its use in conjunction with the adrenal cortical hormone, or pituitary hormone, in dynamic states particularly of the circulation, is indicated.

Studying the calcium question further, we find that the blood calcium is contained entirely in the plasma, and appears in two forms: A diffusible Ca, and non-diffusible Ca, each about 4.5 mg. per 100 cc. The diffusible will pass thru a dialyzing membrane, and would be able to pass thru the living capillary wall or cell membrane. The non-diffusible would not. Of the diffusible 4.5 mg. Ca only about 2 mg. is ionized or electrically charged and probably represents the vitally active form of calcium while the insoluble forms of calcium such as the phosphates and carbonates go to supply the structural framework of the body.

Thus we see that the immense amount of body calcium is mobilized in the ionized state in a very small amount by some physiologic agent that must not be cumulative to avoid too great a solubilizing action. Such an agent is ideally found in Vitamin C which is not stored in the tissues in a supply greater than that which would suffice for 2-3 weeks, after which period there set in symptoms of scurvy. Also, it is a sugar which is readily burned or excreted in the urine. The average total of ionized calcium in the blood stream if calculated at five liters, would be about 100 mgs. or about the daily consumption of Vitamin C. The rate of excretion of cevitamic acid above those amounts would vary with the calcium needs of the body. Thus, in tuberculosis where healing occurs by calcification entailing the mobilization of calcium to the lesion, the excretion of Vitamin C is markedly reduced. Vitamin C is also uniquely fitted to avoid protracted storage in the tissue. Just as parenteral calcium is thrown out almost completely in 72 hours, so also is the structure of cevitamic acid so labile that it is most easily oxidized or reduced and is in addition autooxidizable, thus requiring continuous replacement. In fevers the Vitamin C requirement rises rapidly and hemorrhagic processes complicating protracted illnesses have been viewed from the angle of relative depletion of Vitamin C. Thus Calcium Cevitamate is not merely a mixture of two similarly acting substances, but the finished product of the proper vehicle for calcium where physiologic action is required, and marks a step forward in calcium therapy.

Aside from its vehicle action for calcium, Vitamin C apparently plays a role in the endocrine set-up. Its occurrence in the pituitary in larger amounts than in

other tissues, suggests a relationship there, and its adrenalin stimulating action speak for an endocrine influence.

SUMMARY

1. The parallelism of calcium and Vitamin C action leads to the assumption of a community of action.
2. The chemical properties of cevitic acid would

indicate that it is the stabilizing agent for calcium in the body, participating in absorption and the maintenance of the ionized calcium in serum calcium.

3. A new therapeutic agent for calcium therapy has evolved which possesses the marked advantages of greater solubility, absorbability and complete calcium action.

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The Passage of Gall Stones Through the Sphincter of Oddi*

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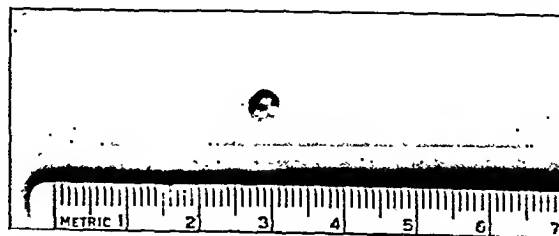
THE search for gall stones in the feces, among the procedures to establish a diagnosis of Cholelithiasis has been regarded as practically useless for several decades and, beginning with the development of the modern roentgen method of gall bladder visualization, has usually been omitted. This paper reports three patients from whose stools gall stones were recovered which passed the sphincter of Oddi during attacks of pain in the right upper quadrant associated with jaundice. An attack of colic during convalescence from cholecystectomy prompted the search for stone in the first patient, while in the second deliberate experimentation with antispasmodic drugs instituted the methodical examination of all stools. The third patient, a physician, in whom the diagnosis of gall stones was only suspected, examined the stools for corroboration.

Case 1. A 70-year-old woman had her first attack of epigastric distress three months before coming to operation. Four succeeding attacks occurred, some of greater severity, with characteristic right upper quadrant pain, requiring morphine for relief, one accompanied by mild icterus.

Examination, three weeks, later, revealed only mild tenderness over the gall bladder region. The gastro-intestinal

investigation was completely negative except for two non-visualizations of the gall bladder by the oral method.

At Cholecystectomy, the gall bladder was found to be small, thickened and adherent to the liver and and was dissected free with difficulty. It contained some thick dark bile and about 27 stones, 20 of which were dark brown, soft, and of grapeseed size, while the remainder



Gall stone recovered from stool of patient at termination of an attack of colic and jaundice which developed eight days after operative removal of gall bladder.

were half again as large and firm. Laid on a film and X-rayed, none cast shadows.

On the eighth post-operative day, the patient complained of abdominal distension with mild epigastric burning; the latter increased in intensity. In 48 hours the patient was moderately jaundiced, the stools were light yellow and the urine contained excess of bile. The following day excre-

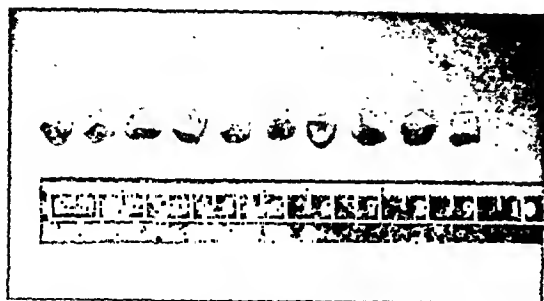
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ciating non-radiating colicky pain in the epigastrium developed and persisted with intervals of greater intensity. The pain was only mildly improved by atropin and benzedrin and was finally controlled by morphine without recurrence. The jaundice became deep and the stools acholic. All stools were examined for stones and on the fourteenth post-operative day, 6 days after the attack, in the last acholic stool one grape-seed sized stone was recovered identical with those present in the gall bladder at operation (Fig. 1). Bile appeared in the next stool. No



Gall stones recovered from the stools of patient 2.
(About $\frac{1}{2}$ actual size)

other stones were found. The remainder of the convalescence was rapid and uneventful.

Case 2. A woman of 60 years had been ill for two years with cardiac disease requiring treatment with amyl nitrite and later digitalis. On November first, 1937, she developed symptoms, "which were quite different from her heart attacks" and which she had had only twice before: "severely in February, 1937, for six hours and less severely a month later." The third attack began with an epigastric discomfort several nights in succession for which the physician was not called until the third evening. The patient was then slightly jaundiced, had a fever of 100 degrees, was tender in the epigastrium with right upper rectus rigidity and bile excess in the urine. The low-grade fever, considerable toxicity, increasing jaundice and light colored stools continued five days, and receded by the fourteenth day. A film, without dye, of the gall bladder region revealed no calcified shadows. The diagnosis was Acute Cholecystitis.

The patient then began to have nocturnal attacks of chill and fever with recurrence of jaundice. The temperature rose above 102 at night and dropped to normal by morning. This was repeated four times from November twentieth through the twenty-fifth and justified a diagnosis of Common Duct Stone. The patient was clear mentally in spite of these sharp bouts and felt less sick than during the earlier time with lower fever. Operation was thought unwise because of the cardiac condition.

Benzedrin and magnesium sulphate were given as follows:

	Benzedrin	Mag. Sulph.
11 20	10 mgm.	
11 21		Z 1
11 24	20 mgm.	Z 1
11 25	30 mgm.	

A short period of low fever and slight jaundice without chill recurred 11 27-11/28. Then suddenly 12/1/37 the patient felt and seemed much improved. The inconspicuous character of the pain at all times should be stressed.

A consistent search for stone in the feces was begun and continued for a month. Calculi were found as follows:

Date	STOOL EXAMINATIONS	Number of Stools	Color	Calculi
11/13-11, 19				
11/21			brown	0
11/23			gray	0
11/24			clay	0
11/26			clay	0
11/28			yellow	0
		1	light brown	0
12/1		1	clay	0
12/2		2	putty color	0
12/3		1	putty color	0
		1	putty color	4
		1	yellowish	2
12/4		1	yellow	0
		1	brown	1
12/5		1	"	0
12/6		2	"	0
		1	"	1
12/7		1	"	0
12/8		1	"	1
12/9		1	"	0
12/10		1	"	1
12/11		1	"	0
12/12		1	"	0

Ten in all were recovered and, as is noted, by no means in consecutive stools. The photograph shows the uniform size of these stones and the definite facetting. (Fig. 2).

Case 3. A well-nourished woman of 62 years, a physician, gave a gastro-intestinal history of one attack of epigastric pain 30 years previously, diagnosed Acute Gastritis, and a long-succeeding period of achlorhydria for which she took dilute hydrochloric acid.

One night, six hours after an ordinary dinner, the patient awakened with epigastric distress, dull and burning, accompanied by nausea and followed within three hours by vomiting. This episode was of about 10 hours duration. For the next few days the patient was unable to eat more than the simplest carbohydrates without precipitating epigastric distress, nausea and vomiting. When, finally, even water was not tolerated and the patient became dehydrated, a physician was called.

At this time, on the sixth day following the first appearance of symptoms, the patient was mildly jaundiced and had definite tenderness in the right upper quadrant. The stools were light and the urine dark with bile. The icterus index was 14. A few stools became acholic. The clinical diagnosis was Common Duct Obstruction. It was suggested that the stools be watched for stones. Nine small faceted



Seven of the nine stones recovered from the stools of patient 3. The remaining two were of the size of the smallest of these. The gall bladder, at operation, was half full of similar sized stones.

stones were recovered in the next five days. (Fig. 3). Some of them, when photographed, cast shadows on X-ray films. Altogether the attack lasted ten days. Subsequently films, following the dye by mouth, failed to visualize the gall bladder or any calcifications. At operation, a thickened gall bladder, half full of stones of the size and shape as shown in Figure 3, was removed. No stones were found in the common duct, though thorough search was made.

The recovery of gall stones from the feces of three patients, who presented themselves for diagnosis with-

in a short time interval, introduces the query if gall stones do not pass the sphincter of Oddi more frequently than is generally believed. It must be admitted that stones of pea-size or under could pass the relaxed sphincter (1, 6). Recent textbooks (3, 11, 15) mention this possibility and the older clinicians, who did not have X-ray at their command, give varying percentages of recovery of calculi from feces. Rolleston (13) states that biliary calculi "not uncommonly" pass when an attack of biliary colic is precipitated at the beginning of a course at Carlsbad, and adds that Kehr (7) puts the recovery of biliary calculi from feces as high as 25%. **Mayo Robson (12), on the other hand, states that they are seldom found. Most clinicians in the last two decades, though concerned with refinements for diagnosis, such as microscopic increase of crystals in duodenal drainage and the origins of different bile fractions, neglect or scorn gross stool examination for stone (2, 4, 8, 9, 11). In contrast, the lay public is always finding and bringing, bottled in alcohol, inconsequential exhibits from the stools and have, in times past, when olive oil was supposed to cure gall bladder disease, brought in "stones" shown to be nothing but inspissated oil. The patient properly instructed in the technic of how and what to look for would, no doubt, cooperate.

One may ask, if Kehr's quoted statistics are right, why stones are not more frequently found when searched for. Aside from the obvious explanation of their being missed or unrecognized when very small, two factors may account for this. Only stones in the common duct could pass into the duodenum and it is not always easy to make a differential diagnosis between stone confined to the cystic duct or gall bladder and common duct stone. Secondly, after stone enters the intestine, the delay in that tract is variable. Although in two of our cases stones were found when the stools were still claycolored or very light, in the second, six came down slowly over a period of days. Instances are cited of small gall stones which must have tarried in the bowel a long time and which have formed the center core of fecoliths, which have finally obstructed the bowel (14). In suitable cases where a search is to be made a saline cathartic is probably indicated. Magnesium sulphate by mouth should be as effective as Carlsbad water after an attack of colic, and, especially in the presence of achlorhydria, may be as relaxing to the duodenum as by instillation through the duodenal tube (16).

Another surmise suggested by our unoperated patient is whether a fistula could possibly have been present to permit the passage of stones into the bowel. The patient was unaware of a long-standing history of gall-

* See Ref. 13, p. 790. The authors could not verify this figure. Hans Eppinger in his book, "Die Leberkrankheiten," Julius Springer, Vienna, 1937, gives the following percentages of the frequency of the passage of gall stones into the bowel:

Goldammer	5.2%
Fink	11%
Kehr	9.3%

Whether these figures include stones passed through artificial as well as natural opening is not clear from Eppinger's text, but from a work of Kehr's, "Die Praxis der Gallenwege Chirurgen," Munchen, J. F. Lehmann, 1913, p. 214, it seems likely his 9.3% referred to stones passing through the sphincter of oddi, not through false passages.

tract disease. Judd and Burden (5) have stressed the long duration and severity of symptoms in patients in whom they found internal biliary fistulae at operation. One must however balance against this Naunyn's (10) statement that ulcerations of gall stones into the intestine may occur in 75% of patients without symptoms! In two other patients, recently seen by one of us, whose histories are not given and who had proven internal biliary fistulae, the attacks preceding the passage of stone were very severe and prolonged. In one the stone recovered measured 1½ by ¾ inches. To the authors it seems more likely that the ten stones found in the second patient reported herein passed the common duct sphincter.***

Recognition of this latter possibility not only allows of an explanation for an attack of severe distress resembling gall stone colic occurring but once in the life of an occasional patient, in whom thereafter by every means at our disposal no further gall stones are demonstrated, but stimulates to a systematic search for stone in the feces, if there is a reasonable suspicion that common duct stone is present. If stones pass the sphincter of Oddi fairly frequently, it permits greater hesitation in patients unsuitable for operation for other reasons, especially when these patients are advanced in years. A trial period of drugs of the duodenum or sphincter relaxing types could be instituted before advising difficult or even dangerous common duct surgery.

In closing, it must be stressed that the recovery of gall stones from the feces in no way assures that all stones have been evacuated from the biliary tract. Operation will of course remain, in the vast majority of patients, the surest method for the removal of gall stones and, when the gall bladder is seriously diseased, the most effective way of dealing with it.

CONCLUSIONS

1. The authors have reviewed the case histories of three patients from whose feces gall stones were recovered following attacks of right upper quadrant pain with jaundice. These stones were small enough to have passed through the sphincter of Oddi and did so with certainty in all three.

2. A short discussion follows, mentioning the literature on the relative frequency of the passage of gall stones through the natural openings and the neglect of the search for stone in the feces as a diagnostic procedure.

3. It is suggested that where stone in the common duct is suspected, evacuation into the duodenum by suitable drugs may be tried in suitable cases before difficult or dangerous common duct surgery is instituted.

4. Finally it is stressed that the recovery of gall stones from the feces does not guarantee complete evacuation of stones from the biliary tract and that surgery remains the surest method for their removal and the most effective for dealing with a seriously diseased gall bladder.

***Autopsy recently confirmed this judgment. No biliary fistula and no stones in the common duct were present. A considerable number of faceted stones like those in Fig. 2 were present in the gall bladder.

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Infra-Red Photography of the Abdominal Wall in Portal Cirrhosis of the Liver*

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SINCE the infra-red photographic plates are made on a production basis, this type of photography has assumed considerable prominence in scenic photography, industry and science. Very little expense is involved in the equipment except the specially prepared infra-red sensitive plates, which cost somewhat more than the ordinary photographic plates or films. Any ordinary good camera, equipped with plate-holders not transparent to infra-red rays, can be used. However, since the infra-red plates are sensitive to the violet and blue regions of the spectrum and to ultra-violet rays, it is

Since the infra-red rays penetrate the superficial layers of the skin, infra-red photography may show some pathologic condition of the subsurface of the skin not visible to the naked eye or on the ordinary photographic plate or film. Of particular value in medicine is the visualization of superficial veins, their course and the demonstration of possible enlargement, tortuosity and or anastomoses. The arteries remain invisible. The demonstration of the superficial veins of the extremities with the aid of infra-red photography has added much to our knowledge of peripheral vascu-



Plate I. Ordinary photograph on the left (picture B) and infra-red photograph on the right (picture A) of the abdomen of a normal individual. Note the absence of demonstrable veins on picture B over the dome of the abdomen.

necessary to use a filter which absorbs these rays, but transmits the infra-red ones. A good source of light for in-door photography can be supplied by an incandescent tungsten filament or a photoflood lamp.

The infra-red rays, because of the greater wave length, are absorbed by and reflected from various surfaces differently than the visible rays. They also have the power to penetrate hazy or opaque layers and substances. Thus are explained the remarkably clear long-distance scenic pictures obtained by this method of photography.

lar diseases, especially varicose veins. Other uses, to which this method of photography has been applied in medicine include (a) the demonstration of the contour and size of the pupil as seen through a dense cornea (1); (b) photography of thicker microscopic sections and of injected gross specimens, showing details of internal structure not always visible on ordinary photomicrographs or films (2); (c) photography of blood samples in order to determine the presence of CO-hemoglobin or reduced blood (3).

We attempted to demonstrate changes of the veins of the abdominal wall in portal cirrhosis of the liver. In this condition there is established a collateral circulation because of the portal hypertension which accom-

*From First and Third Medical (Tufts teaching) services Boston City Hospital. Aided by the Charlton fund of Tufts College Medical School. These photographs were a part of our scientific exhibit at the A. M. A. convention at Atlantic City in June, 1937. Submitted February 21, 1938.



Plate II Eight months pregnancy The infra-red photograph (on right) shows enlargement of the superficial veins of the abdomen. Note the lack of anastomoses. On the left is an ordinary film of the same case showing no demonstrable superficial veins.

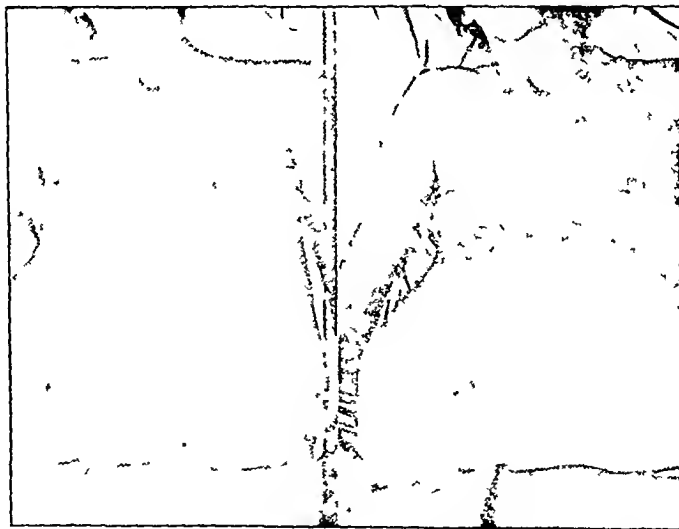


Plate III Cardiac cirrhosis with ascites. On the right is an infra-red photograph showing enlarged dilated veins with a coarse network of anastomoses. On the left is an ordinary film of the same case showing no demonstrable superficial veins.



Plate IV. Cirrhosis of the liver with ascites. On the right is an infra-red photograph of the abdomen showing enlargement and tortuosity of the superficial veins. Note the fine network of anastomoses. On the left is an ordinary film of the same case showing no demonstrable superficial veins.

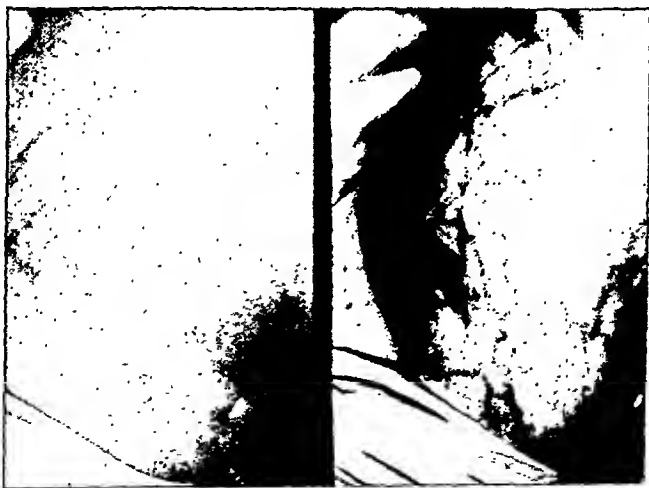


Plate V. Cirrhosis of the liver without ascites. On the right is an infra-red photograph of the abdomen showing enlargement and tortuosity of the superficial veins. Note the fine network of anastomoses. On the left is an ordinary film of the same case showing no demonstrable superficial veins.

anies it whether ascites is present or not. In order to establish the pathogenicity of a change in the pattern of the superficial abdominal veins we have photographed the abdomen of normal individuals, patients with various abdominal diseases, those with cardiac decompensation, some pregnancies in various stages as well as patients with definite or questionable portal cirrhosis of the liver.

The following technique is used by us. With the patient in the erect or recumbent position, the abdomen is exposed. For illumination two kodalites with 500 watt lamps are used, placed one on each side of the patient at a distance of about three feet. We use an Eastman clinical camera equipped with an astigmatic lens over which is placed a No. 25A Wratten filter. The focussing is done with the filter in place. There should be no movement or breathing while the photograph is taken. The Eastman Kodak infra-red plates loaded and developed in total darkness have proved

ordinary photographic plates or films. Whether the veins are visible or not, infra-red photography demonstrates these veins as enlarged, at times tortuous dark lines, showing few or no anastomoses. For illustration we show representative cases of pregnancy (Plate II) and cardiac cirrhosis with ascites (Plate III).

In the presence of portal hypertension, as in portal cirrhosis of the liver with or without ascites, new anastomoses between the portal and general venous systems are established. Thus varicosities of the veins of the esophagus, cardiac end of the stomach, and of the rectum are developed. There are also established some anastomoses between the veins of the portal system and those of the abdominal wall. The result is enlarged, distended and often tortuous veins of the abdominal wall with many anastomoses. The amount of the collateral circulation, involving the superficial veins of the abdominal wall, depends primarily upon the degree and duration of portal hypertension. Since in



Plate VI. Early cirrhosis of the liver. On the right is an infra-red photograph of the abdomen showing enlargement of the superficial veins with some anastomoses especially in the right upper quadrant. On the left is an ordinary film of the same case showing no demonstrable superficial veins.

satisfactory in our hands. Exposure time under these conditions is one second. The plates should be fresh and stored in an ice box or refrigerator, as they may become fogged by heat. For comparison we also photograph the abdomen using the orthochromatic plates without the filter.

The infra-red photograph of the abdominal wall in normal individuals shows a few narrow, straight, superficial veins in the groin and possibly over the lateral aspects of the abdomen. There are no demonstrable veins over the dome of the abdomen. On plate I, picture A is a representative infra-red photograph of a normal abdomen; for comparison, picture B is an ordinary photograph of the same case. In cases of increased intra-abdominal pressure due to large abdominal tumors, ascites or in advanced pregnancy, the veins of the abdominal wall are congested, dilated and more prominent. They become demonstrable by infra-red photography over the dome of the abdominal wall. Not infrequently they become visible on

portal cirrhosis of the liver the interference with the venous flow in the portal vein is of long duration and considerable degree, the veins of the abdominal wall are enlarged, tortuous and form numerous anastomoses, all of which can be demonstrated by infra-red photography. Dependent not only upon the duration of the disease, but also upon whether the portal circulation is compensated or not, the number of blood vessels and their anastomoses demonstrated by infra-red photography, varies from case to case. In well developed portal cirrhosis of the liver there is a large network of superficial abdominal veins on an infra-red photograph. Some of the larger ones may be visible to the naked eye or on ordinary photography. However, the true topography of these veins can be demonstrated by infra-red photography only. Plates IV and V show representative cases of advanced cirrhosis of the liver. One can see the numerous superficial veins and free anastomoses between them, while the accompanying ordinary photographs show none at all. Of greater

clinical importance is the demonstration of a similar but less marked network of superficial veins in early or doubtful portal cirrhosis of the liver. Such demonstration may clinch the diagnosis of cirrhosis in doubtful cases. Plate VI shows a representative case of this type. On the infra-red photograph one notices a considerable number of superficial veins, while the accompanying ordinary photograph reveals none. Furthermore, since portal cirrhosis of the liver is a progressive disease the graphic record of an infra-red photograph of the abdomen may be compared with a later one, which in this disease would show an increasing network of the superficial veins.

Cognisant of the fact, that the early diagnosis of portal cirrhosis of the liver is extremely difficult and at times impossible, we believe that infra-red photography offers a method of early diagnosis. On the other hand, the absence of an enlarged network of superficial veins of the abdominal wall does not rule out portal cirrhosis of the liver in the early stages. We feel, however, that in cases which appear as advanced cirrhosis, the absence of enlarged veins of the abdominal wall rules out this disease. In our experience,

metastatic carcinoma of the liver, diffuse abdominal carcinomatosis and gumma of the liver show no increase in superficial veins on infra-red photographs. This photographic demonstration can be used in differential diagnosis of portal cirrhosis of the liver.

SUMMARY AND CONCLUSIONS

Infra-red photography of the abdominal wall by visualization of the superficial veins of the abdomen presents a true pattern of these veins. This pattern varies in health and in abdominal disease. The pattern of the superficial veins of the abdomen in cirrhosis of the liver is pathognomonic of it. As such, it can be used to confirm a suspected case of this disease. However, the absence of the characteristic vein pattern does not rule out early portal cirrhosis of the liver.

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The Efficiency of Several Germicides and Antiseptics on the Oral Mucosa*

By

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ACCORDING to observations made by Arnold and Stuart (1935), the lips apparently are a primary seeding zone for the mouth. The narrow zone of contact of the lips is an area which when inoculated with organisms, seems to furnish an unlimited supply for almost continuous contamination of the oral cavity.

It, therefore, was conceded that this zone would be a desirable one to make use of in order to test the efficiency of various germicidal solutions to be used on the oral mucous membrane. It was our aim to find an agent which would be the most efficient and whose action would continue for the longest period of time. The efficiency of germicidal agents on the skin has been reported in numerous papers. There have been, however, relatively few reports dealing with the direct application of a germicide to the oral mucous membrane.

Rodriguez (1928) published results of his experiments using the under side of the upper lip as the zone of application for the germicide. He used cotton rolls on both sides of the upper maxilla for a two fold purpose. It served as a dam against the outflow of Stenson's duct and prevented contact of the mucosa and teeth about the angles of the mouth. He used Mercurochrome 2% aqueous solution, Mercurochrome 5% in 50% alcohol, Mercurochrome 2% in alcohol, acetone mixture, Tincture of Iodine, and

glycerine 3.5%, and Tincture of Iodine and glycerine 1.75% and Iodine in alcohol 3.5%.

He concluded 3.5% Tincture of Iodine was too irritating on the oral mucosa but efficient. The 3.5% Iodine and glycerine mixture was effective and devoid of irritating effects. This solution has been used for a number of years in dental practice. The 1.75% Iodine and glycerine mixture is the lowest dilution which can be used and still be effective. Certain people, however, show some irritation upon using Iodine on the mucosa. Mercurochrome 5% in 50% alcohol was effective. It seems to have selective action for *Staphylococcus albus* but is irritating. The alcohol-acetone solution of Mercurochrome was too irritating.

In conclusion he states that Iodine is the most effective germicide to use on the oral mucosa in the presence of the organic elements constantly present on the surface of the mucous membrane of the mouth although he states that it was irritating to some people.

TECHNIQUE

The narrow zone of contact of the lips was numbered "zone 5". This zone was divided into four areas i. e., the left upper half was numbered area 1, the right upper half area 2, the lower left half area 3, and the lower right half area 4.

Sterile swabs were moistened with sterile normal saline solution and control swabs taken from zone five on areas 1, 2, 3, and 4. The swab was thoroughly rubbed over an agar plate streaking the plate across

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one way and then the other to insure as equal a distribution of the organisms as possible.

The average number of colonies obtained on control plates from zone 5, ranged from 600 to 10,000. As a matter of interest, zone 5 was cultured three times in succession, the average number of colonies on the first set was 1,550, the second set 2,280 and the third set 4,400. This experiment was repeated six times with the same result, that is, the second set showed a higher average than the first and the third set a higher average than the second.

In testing the germicidal solutions, a sterile swab was moistened with the agent and rubbed over the lips and zone 5. Then at intervals of 1, 3, 4 and 5 minutes, swabs were taken of zone 5 on area 1 in 1 minute, 2 in 3 minutes, 3 in 4 minutes, and 4 in 5 minutes and rubbed on agar plates as mentioned previously. In cases where the agent tested was found to reduce the bacterial count from 75-100% the duration in time of antiseptic action was determined.

A germicidal control plate was made in each experiment in order to ascertain whether or not any inhibition of growth was caused by the amount of germicidal agent taken up on the swab. A swab was taken from the lips immediately after the application of the agent and rubbed over an agar plate, then a drop of a liquid culture of *Staphylococcus albus* was spread on this plate. In no case regardless of the antiseptic used, was any inhibition of growth observed.

All plates prepared in this work were incubated for forty-eight hours and then counts were made using a Frost plate counter aided by a 9x hand lens. The total

number of colonies obtained from zone 5 both before and after the application of the antiseptic agent was determined and the percentage of reduction computed in this way. In testing of the germicides at least ten trials were made with each on as many different subjects as possible except in cases where the agent was found to be too irritating. The germicide found to be the most efficient and without too many objectionable qualities was tested twenty times on as many different subjects as possible. The following chart indicates the method used in computing the results:

CHART I			
Controls		Zone 5	Antiseptic Agent
Area 1	1,440	Area 1, 1 minute	50
Area 2	3,120	Area 2, 2 minutes	0
Area 3	2,880	Area 3, 3 minutes	35
Area 4	1,920	Area 4, 4 minutes	300
Total	9,360	Total	385
Percent reduction 95.9%			

Types of organisms cultured from Area 5 in order of frequency:

1. *Staphylococcus albus*.
2. Two types of minute colonies.
 - a. Larger ones consisting of either Gram positive diplococci, diphtheroids or Gram negative diplococci.
 - b. Minute pin point colonies which may be either streptococci, diplococci or diphtheroids. Some of the streptococci proved to be *Streptococcus lactis*, *Streptococcus salivarius*, others seemed to be dissociated forms. The growth of the dissociated forms is extremely

CHART II

Agents	Type of Solution	Average Reduction of Colonies in 5 Minutes	Duration of Action	Comments
Sod Perborate	30 grs in 4 oz warm water	85%	10 Minutes	More effective against staphylococci than streptococci
Hydrogen Peroxide	3% commercial solution	75%	10 Minutes	"
S T 37	Liquor Hexylresorcinolis 1 1000 solution	35%	—	In several subjects there was no reduction in count
1 Disodium salt of 2 7-dibromo-4-hydroxymercuriflorescen	2% aqueous solution	50%	—	Stain objectionable
	2% alcohol-acetone tincture	90%	30 Minutes	Solution too irritating, also stain objectionable
2 Sod salt of ethyl mercurithiosalicylic acid	1 100 alcohol acetone-aqueous monoethanol amine tinc	65%	—	Too irritating No reduction in count in several subjects
Neutral acriflavine.	1 1000 in normal saline	55%	—	
Phenyl mercuric nitrate	Sat aqueous solution (0.06%)	0%	—	Has a phenol coefficient of 625 and is non-toxic
Phenyl mercuric nitrate	Alcohol-acetone aqueous solution (0.034%)	50%	—	Too irritating
Glycerinated Iodine solution 3 5%	50% Tincture of Iodine, 50% glycerine	95%—* 100%	30 Minutes	Some subjects complained of irritation
"	25% Tincture of Iodine, 75% glycerine	75%	20 Minutes	"
Mineral Oil, Iodine solution 3 5%	50% Tincture of Iodine, 50% Mineral oil	95%—* 100%	40 Minutes	Longer action and less irritating Oiliness objectionable to some
Liquor Antisepticus	National Formulary VI	50%	—	
3 4 nitro 5-hydroxy-mercuri-ortho cresol	1 200 alcohol-acetone aqueous solution	95%—* 100% *	2 Hours	Only a very slight irritation to some No untoward after effects
"	1 500 Special Experimental mouthwash, Peppermint flavor	75%—* 85% *	1½ to 2 Hours	

* Cotton rolls used to restrict flow of saliva 1 Mercurochrome 2 Merthiolate 3 Metaphen

limited on media and growths in liquid cultures are difficult to keep alive.

3. Large wrinkled colonies, translucent in character and consisting of Gram negative diplococci and fours.
4. *Staphylococcus citreus* and *Staphylococcus aureus* occasionally.
5. *Subtilis* occasionally.
6. *Sarcina* occasionally.

It was observed with all of the germicides that there seemed to be more selective action against staphylococci than streptococci. In determining the duration of time which the germicides on the oral mucosa are effective, it was observed also that the staphylococci are inhibited for a longer period of time than the streptococci. The streptococci colonies appear in larger numbers sooner than the staphylococci colonies, returning suddenly and gradually increasing in number.

It was also observed that even in cases where some of the agents used were very effective, there would be an occasional individual whose tests indicated little or no antiseptic action had occurred on their oral

mucosa. This may have been due to the fact that some were not able to restrain the flow of saliva as well as others or as said by Hill and White (1930)—“We noted a variation in the ease of sterilization among different individuals. The skins of two laboratory technicians were not sterilized in either of two tests on each individual.” In the case of 4 nitro-5-hydroxy-mercuri-ortho cresol (Metaphen) however, we found this to be the minimum as compared to all other agents. Chart II shows the results obtained in the series of experiments.

CONCLUSIONS

The results of this study indicate that Tincture of 4-nitro-5 hydroxy-mercuri-ortho cresol (Metaphen-1 to 200) is the most effective agent both in its germicidal action on the oral mucous membrane and in the duration in time of antiseptic action. The tincture is convenient to use because there is little, if any, irritation, the color marks the area treated and it is very readily washed off with water.

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Primary Carcinoma of the Liver*

By

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THE dictum of Virchow which states that, “such tumors as are the frequent sites of secondary tumors rarely exhibit the primary type” seems particularly applicable to the liver. During the past ten years, in the wards of the Buffalo City Hospital, twenty-four cases were studied and diagnosed as primary carcinoma of the liver. Only twelve of these cases were proved by post-mortem examination and four by biopsy. We shall limit our discussion in this communication to the proven cases. In this same period of time 116,622 patients were admitted to the wards of the Buffalo City Hospital and in 2099 of these malignancy was diagnosed. Likewise, over this period of time about 4,400 autopsies were performed of which only twelve were primary carcinoma of the liver.

The statistical reports of White, Price and Leeds; Counsellor and McIndoe (1), would indicate that a comparatively small number of cases present this lesion. Our series bears this out and shows also that the disease occurs more frequently in the male sex, since we have observed fifteen males to one female. This fact is of interest in view of the striking contrast of sex incidence in carcinoma of the gall bladder, which is more common in the female. Likewise in metastatic carcinoma of the liver the incidence seems slightly higher in females.

Carcinoma of the liver, like most malignant diseases, occurs most often in the fourth to the sixth decade of life. Egge (2) reports the average age in his series as 57.2 years. We have observed the average age to be slightly lower, being 49.4 years.

It is apparent from the following table that the

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greatest number of our cases occurred in the accepted age groups:

Age Groups	Number of Cases	Per Cent
30-35 years	2	12.5
35-40 years	0	0
40-45 years	2	12.5
45-50 years	4	24.8
50-55 years	2	12.5
55-60 years	2	12.5
60-65 years	3	18.6
65-70 years	1	6.25

The youngest case in our series was 34 years of age and the oldest 70 years. Prescott (3) reported a case of congenital carcinoma of the left lobe of the liver in an infant of five months, while Ribbert (4) reported a similar congenital malignancy in a four month old baby.

PATHOLOGY

A clinical classification of primary carcinoma of the liver which is frequently used includes:

A—*Primary, Massive Carcinoma* in which the cells are large and polyhedral and the liver attains a massive size. Only one case of our series was of this type.

B—Two of our cases were *primary infiltrating or diffuse* type.

C—Five conformed to the *nodular* or *multiple* types.

D—Eight cases in our series, seemingly developed in a cirrhotic liver, since elements of both were present.

Pathologically it would seem better to classify these tumors histogenetically. Primary carcinomata have only two sources of origin: (1) the parenchyma or liver cell and (2) the epithelial lining of the ducts. Mixtures of these two types have been observed, however. In the liver cell type, the lesions are usually multiple with a primary source but individual lesions are fairly sharply circumscribed. This type is very cellular and has little stroma, while umbilication and central necrosis occur early. A type of growth occasionally seen is that of a huge liver with decided increase of connective tissue, suggesting an exaggerated proliferation of the bile ducts, which crowd the lobular structure to the point of atrophic disappearance. This type has been termed Banti's Disease when associated with splenomegaly, and in previous years, was also referred to as "Cirrhosis carcinomatosis."

CLINICAL FEATURES

The clinical manifestations in our cases were quite variable. Pain was a rather constant feature, being present in eleven of the group and located either in the epigastrium or the right upper quadrant of the abdomen. Anorexia and emaciation was present in all instances, but pronounced in only six of the entire group. Jaundice was rather infrequent and occurred in six

cases, while subclinical jaundice was present in an additional four. Nausea, emesis and constipation were infrequent symptoms. The liver was definitely enlarged to palpation in every case and was nodular in more than half of them. The spleen was palpable in only four cases of the entire group. Ascites occurred in six cases; the fluid removed from the abdominal cavity was exudative in character, and tumor cells were recovered from the centrifuged sediment in three different cases.

LABORATORY FINDINGS

There has been some reference (5) to the presence of fever and leucocytosis in the latter stages of this malady. In six or thirty-six and a half per cent of our cases leucocytosis was present. In no case did it go above 20,000 cells and in the majority of cases, it varied between 10,000 and 14,000. Fever was observed throughout the course of the disease in only six cases, but was present terminally in an additional six. The blood urea N was normal in our entire group; in none was it higher than 20 mm. per 100 cc. of blood. The Wassermann reaction was positive in only two of our cases. The blood sugar was within normal limits in all instances.

COURSE

The course of the disease in our group was rapid and fatal. The majority of our patients presented distinct clinical manifestations of the disease within one year of their initial complaint. More than half of the group, however, had symptoms for less than six months. Thirteen of this group were observed in the hospital less than six weeks prior to their death, indicating the rapidity of this disease.

METASTASIS

Metastasis from the primary liver focus occurred usually by way of the regional lymph glands, but extra hepatic metastases have been found in about twenty per cent of cases reported in the literature (5). Our findings agreed with this, for we found that fifty per cent of our cases showed metastasis in the regional lymph nodes, while in one instance each, there was metastasis to the pericardium, lung and mesentery.

SUMMARY

We have reviewed sixteen cases of primary carcinoma of the liver diagnosed clinically and confirmed pathologically. We have also briefly presented the clinical manifestations of this disease.

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The Use of Hydrated Magnesium Trisilicate in Peptic Ulcer*†

(Preliminary Report)

By

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HYDRATED Magnesium Trisilicate was introduced into therapeutics in 1936 by N. Mutch (1, 2, 3). The first to write about the subject in the American literature was Levin (4). He used the trisilicate of Magnesium in a mixture with other antacids to treat peptic ulceration. Hurst (5) is the only other author who has referred to the clinical use of this substance.

Because, according to Mutch, the antacid power of Hydrated Magnesium Trisilicate is sustained for hours even in the presence of excess of acid, because its adsorptive power lasts even for a few days, because it has strong antipeptic powers, because even in large doses it causes neither constipation nor diarrhea, and because it cannot produce alkalosis by absorption of unused excess, I considered this an ideal antacid for use in patients with peptic ulcer. All antacid powders have certain definite drawbacks—the constipation caused by Bismuth and Calcium Salts, the laxation of Magnesia, the secondary rise and tendency to alkalosis caused by Sodium Bicarbonate are well known. For the past two years I have used Colloidal Aluminum Hydroxide preparations with good results and without some of the ill effects expressed above except for very frequent complaints of constipation and two cases of fecal impaction.

In view of the marked relief of symptoms obtained in peptic ulceration with the use of Magnesium Trisilicate I am presenting this preliminary report to stimulate further clinical trial of the powder. My results have been so gratifying that I am replacing other alkalis with this preparation.

I have now used Hydrated Magnesium Trisilicate in 38 private patients having roentgenologically proven duodenal ulcers associated with definite hyperacidity to a test meal, and typical symptoms. The preparation has also been used on several clinic patients fulfilling the same criteria. Due to insufficient time for follow up on the clinic cases I am not including them in this preliminary report. The drug has been used by the patients for from three to six months. The patients were all kept on an ambulant diet. A few had a preliminary rest period at home of from three days to two weeks. In general the routine was the same as I have used for some time except for the substitution of the Hydrated Magnesium Trisilicate in place of other

antacids. The patients received three light meals per day and a glass of milk or milkshake or tea between meals and in the evening. One hour after meals and one hour after the between meal feedings and at bedtime they were given a teaspoonful of the powder. Some bromide or phenobarbital was given if there was excessive nervousness or sleeplessness. Some of the patients also received tincture of belladonna. If there was night pain the patients set their alarm clocks one hour before the anticipated period of distress and took a teaspoonful of the powder at that time. Some of the patients had had ulcer symptom recurrences for many years and had had many types of treatment. Two of the patients had had a gastro-enterostomy for ulcer with recurrence of symptoms but without demonstrable jejunal ulcer. One had been doing well on Colloidal Aluminum Hydroxide but complained of constipation. On changing to the Magnesium Trisilicate he continued to do well and no longer was constipated.

All the patients in this group are improved. Of course, this is the usual response to any new therapy. However, to control psychic factors, the patients were not told that they were receiving a new preparation. I do not hold Magnesium Trisilicate to be a cure for peptic ulceration but merely as a valuable antacid. Antacids are used not to cure ulcers but to control symptoms. The cure of ulcer is a problem of changing the patient's mode of living, thought process and dietary habits so that the factors producing recurrences will not come into play. Of prime significance in the use of this powder is the fact that not a single patient complained that it affected his bowel habits in any way. None of the patients showed symptoms of alkalosis. Hurst (5) has given this preparation in 30 grain doses to ulcer patients and alkalosis has never developed.

I am not presenting a statistical table in this preliminary report. The time the patients have been under treatment is too short and the number of cases is too few for use of any statistical method of evaluating the powder. In my clinical judgment, this is a valuable therapeutic agent which merits further trial.

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*From the Gastro-Enterological Clinic of the Presbyterian Hospital in Newark.

†A supply of Hydrated Magnesium Trisilicate Powder was kindly supplied to the Clinic by Frederick Stearns and Company. That used by the private patients was purchased on prescription.

‡Chief, Gastro-Enterological Clinic, Presbyterian Hospital, Gastro-Enterologist, St. James Hospital in Newark.

§Since writing of article, the powder has been used on 2 cases of gastric ulcer with resulting disappearance of the niche on X-ray.

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Variations in the Level of Serum Lipase in Experimental Pancreatitis*

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BIOCHEMICAL methods available for the study of acute pancreatitis depend for the most part on a study of the distribution of the pancreatic enzymes in the body. In general, these methods have not proved themselves to be specific, nor serviceable in indicating the severity or the course of the pathological lesion. Cherry and Crandall (3) have introduced a method for determining the amount of olive oil splitting lipase in the blood as a means of studying the reaction of the pancreas to experimental procedures. This method has not been hitherto used in the study of the level of serum lipase in experimental pancreatitis.

Claude Bernard in 1856 produced acute haemorrhagic pancreatitis in the dog by injecting bile and sweet oil into the pancreatic duct. Since then many other substances have been used to cause experimental pancreatitis (10, 8, 13, 14, 5, 12). Archibald (1) in experiments on the cat has caused pancreatitis of varying degrees of severity by running bile into the gall bladder, the sphincter of Oddi being contracted by various means and also by inserting a cannula into the pancreatic duct through the ampulla of Vater and running normal and infected bile into the pancreatic duct at a pressure similar to that normally present in the biliary passages.

The pathological findings were recorded by both gross and microscopic examination at various periods after operation. It was found that all grades of pancreatitis from simple oedema to acute haemorrhagic pancreatitis with necrosis could be produced. Chiray, Berdet and Taschner (4) using both a stalagmometric method with tributyrin as a substrate and also a titration method with an olive oil substrate sometimes found lipase normally present in the blood serum of the dog and its amount was increased by the injection of secretin and pilocarpine. Fiessinger, Fernet and Gajdas (7) also using a stalagmometric method with tributyrin as a substrate found more lipase normally present in the blood of the dog than in man and they noted almost as much lipase in the blood of depancreatized dogs up to two weeks after operation. Cherry and Crandall (3) using a modification of the Loevenhart (11) method for esterase with an olive oil emulsion as substrate have shown that following ligation of the pancreatic ducts, division of the pancreas between ligatures and excision of the body of the pancreas, an olive oil splitting lipase appeared in the blood in large quantities while there was no significant uniform change in the amount of serum esterase as measured by the hydrolysis of ethyl butyrate or tribu-

tyrin. They believe that the rapid rise of an olive oil splitting lipase in the blood following pancreatic obstruction, without a corresponding increase in the serum esterase to be good evidence of the specificity of pancreatic lipase. They have also shown that tributyrin hydrolysis is not an index of the presence of true pancreatic lipase and they concluded that the conflicting results of many investigators who used tributyrin and ethyl butyrate as a substrate may be explained by their findings. Several authors (15, 4, 3) have suggested that the term lipase should be reserved for the enzyme acting on the triglycerides of the higher fatty acids while esterases may be defined by their property of hydrolysing the simple esters or mono-esters.

Baló and Ballon (2) have studied the effect on the pancreas of acute and chronic obstruction of the pancreatic ducts. They found that retention of the pancreatic juice caused dilatation of the ducts and acini, with flattening of the acinar cells, and that necrosis might follow.

The purpose of our experiments was to produce a pancreatitis by injecting bile into the pancreatic duct and to follow the change in the level of serum lipase and to see if any relation existed between the height of the blood lipase and the degree of pancreatitis. The duct was not ligated and the pancreatic secretion was permitted to resume its normal flow into the duodenum once the inflammatory reaction had subsided. In this way the back pressure effects on the gland observed by Baló and Ballon were avoided. This procedure simulated more closely the mechanism of production of pancreatitis in man as postulated by Archibald.

METHOD

In these experiments seven dogs were used. They were fed a diet of Purina dog biscuit and as much water as desired. The blood was collected in the fasting state. The method of Cherry and Crandall (3) for determining lipase was used. To 1 cc. of serum were added 2 cc. of a fifty per cent olive oil emulsion* and 0.5 cc. of N/3 potassium phosphate buffer adjusted to pH 7.0. This was then incubated at 37° C. for 24 hours. Then 3.0 cc. of 95% alcohol were added and 3 drops of 1 per cent phenolphthalein. Titration was performed with N/20 sodium hydroxide and the result was expressed in cc. of N/20 sodium hydroxide per 1 cc. of blood serum. The determinations were made in duplicate and control blanks were titrated with each group of determinations. At operation, the main pancreatic duct was located, a fine needle was inserted into its lumen and depending on the size of the dog from two to five cc. of bile aspirated from its gall

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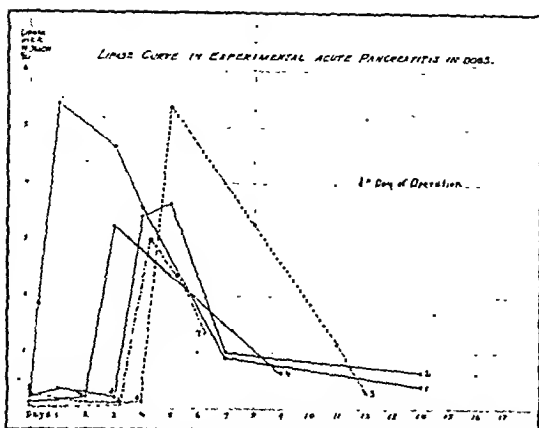


Chart No. 1 shows the course of the serum lipase following injection of normal bile into the major pancreatic duct. From 2-5 cc. of bile were injected.

bladder were injected slowly with a syringe. Immediately following this procedure the pancreas became stained with bile which in most cases penetrated the finer ramifications of the ducts as far as the tail. The surface of the gland became glassy from oedema of the pancreas. Within two or three days all the dogs seemed to have recovered from the shock of the operation.

Chart 1 shows the effect on the level of serum lipase following injection of bile into the duct of Wirsung. In every case a high level had been reached in twenty-four hours and in one dog as early as the sixth hour post-operatively. The amount of lipase was from fifteen to fifty times that of the pre-operative value, which in the dog is very low. After attaining a maximum in from 24 to 48 hours the lipase declined abruptly at first and then more gradually until after 7 to 10 days it had almost returned to normal. Since the pancreatic duct was only slightly traumatized there was nothing to prevent the external pancreatic secretion from resuming its flow into the duodenum once the inflammatory reaction had subsided. The dogs were sacrificed at periods varying from three days to twelve weeks after operation and sections were taken from the head, body and tail of the pancreas for microscopic examination.

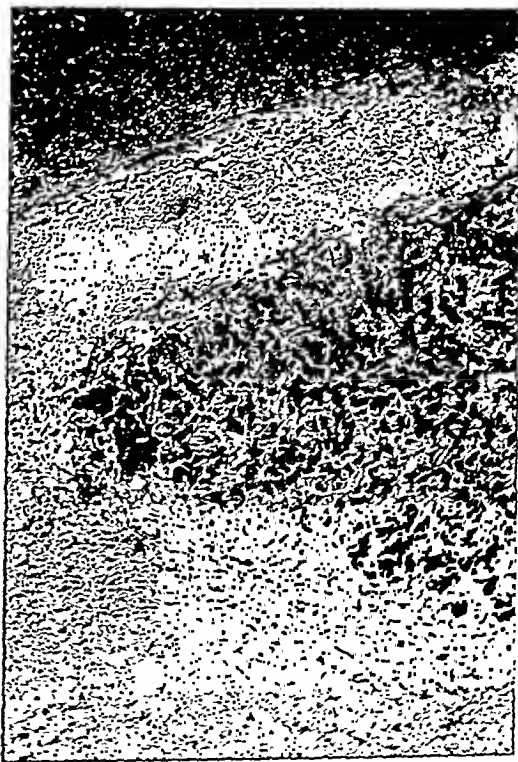
PROTOCOLS

Dog No. 7. Weight 16 kilos. Under avertin anaesthesia 4 cc. of bile were injected into the major pancreatic duct. The pancreas became stained with bile throughout and the gland was slightly swollen before the abdomen was closed. Three days later the dog was again anaesthetized and the abdomen was reopened. On gross examination the omentum was found to be adherent to the pancreas and there were many areas of fat necrosis in the vicinity of the pancreas and duodenum. The pancreas was swollen and firm and a small abscess was found in the body. The pancreatic duct was examined and found to be patent. Microscopic sections showed a marked interlobular inflammatory exudate with evidence of fibroblastic proliferation. There were patchy areas of necrosis of the parenchymal cells, between which the acinar cells were relatively well preserved though the lobules were

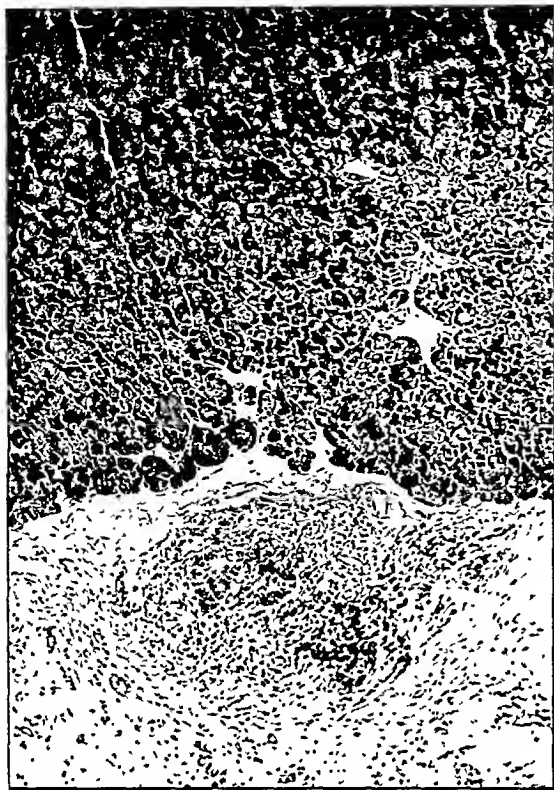
separated by inflammatory exudate. This dog showed the pathological picture of acute haemorrhagic pancreatitis with necrosis. The course of the blood lipase is indicated in Chart 1, and Photomicrograph No. 1 shows a typical section taken from the pancreas.

Dog No. 6. Weight 20 kilos. Intravenous injection of avertin was used to produce anaesthesia. The duct of Wirsung was located and 4 cc. of bile were injected into it with the result that the pancreas was tinged with bile throughout its whole extent. Eleven days later the dog was killed with ether. On opening the abdomen a few adhesions were found between the omentum and duodenum. The pancreas seemed to be normal in appearance on gross examination. No areas of fat necrosis were seen. On microscopic examination sections taken from the head, body and tail of the pancreas showed a slight increase in fibrous connective tissue in focal areas about the ducts and in the interlobular stroma. The tail showed areas of round cell infiltration. The highest value for serum lipase was 2.80 cc. reached three days after operation.

Dog No. 1. Weight 22 kilos. After induction of anaesthesia with avertin, 4 cc. of bile were injected into the major pancreatic duct. The whole pancreas became stained yellowish with bile and before the abdomen was closed the gland was swollen and glassy from oedema. Thirty-eight days later the abdomen was reopened. A few adhesions and some small areas of fat necrosis were noted in the vicinity of the tail of



Photomicrograph No. 1. The section from the body of the pancreas of dog No. 7 shows a marked interlobular and intralobular inflammatory exudate with evidence of fibroblastic proliferation. Areas of necrosis of the acinar cells may be noted.



Photomicrograph No. 2. The section from the tail of the pancreas of dog No. 1 shows a focal area of parenchymal cells undergoing replacement with fibrous connective tissue.

the pancreas. Two cc. of bile were injected into the pancreatic duct and the abdomen was closed. Forty-seven days later the dog was sacrificed with ether. On gross examination the pancreas appeared normal. Microscopic sections showed focal areas of fibroblastic proliferation about the ducts and in the interlobular tissue. Chart 1 shows the course of the serum lipase. Photomicrograph No. 2.

Dogs No. 3 and No. 5 were sacrificed thirty-five and sixteen days, respectively, after operation and microscopic examination showed only focal areas of fibrous connective tissue about the ducts and in the interlobular stroma. Dogs No. 2 and No. 4 who came to autopsy eighty-four and thirty-one days, respectively, after operation showed no definite change in the pancreas. In no case did the pancreatic ducts appear to be dilated.

DISCUSSION AND SUMMARY

Following the injection of bile into the major pancreatic duct there was a prompt rise in the serum

lipase which usually reached a maximum in twenty-four to forty-eight hours. After reaching a peak it subsided abruptly at first and then more gradually until an approximately normal level was reached within seven to ten days post-operatively. The changes found at autopsy varied from a typical acute haemorrhagic pancreatitis with necrosis to a reaction so slight that eleven days after injection of bile into the duct of Wirsung the only changes noted in the pancreas were focal areas of fibrosis and round cell infiltration. In two dogs which showed a high level of blood lipase following operation no significant changes were found in the pancreas at necropsy.

It would appear that different degrees of pancreatitis were produced in the various dogs by injecting bile into the major pancreatic duct. Possibly as McCaughan (11) has suggested, the more severe grades of pancreatitis may be caused by rupture of some of the finer ducts and extravasation of the bile into the parenchymal substance. Undoubtedly other factors exist which may modify the intensity of the inflammatory reaction. For example, the greater the amount of mucin in the bile the less severe is the pancreatitis caused by its injection into the pancreatic duct (9). The rise in the amount of serum lipase in most cases is probably dependent on the amount of oedema or inflammatory reaction produced by the injection of bile.

In dog No. 6 at necropsy, the pancreas showed a relatively slight degree of pathological change though the serum lipase reached a fairly high level after operation. In this dog the inflammatory reaction was probably quite mild and oedema with temporary occlusion of the pancreatic ducts may have accounted for the increased serum lipase.

On the other hand, in the more severe grades of pancreatitis the serum lipase may not rise as high as in the milder inflammatory reactions due to extensive destruction of the acinar cells or obstruction of the blood or lymph vessels. Confirmation of this fact was seen in one patient who was admitted to the hospital with signs and symptoms suggestive of an acute upper abdominal condition. The blood lipase was normal. At operation a hyperacute pancreatitis was found. At autopsy focal areas of necrosis were found throughout the pancreas with marked collapse of the acinar cells. Comfort (6) in a series of twenty-one cases of acute pancreatitis noted one patient in which the serum lipase remained at a normal level.

Increased serum lipase occurs regularly in experimental pancreatitis and its estimation should prove a valuable diagnostic aid to the surgeon in cases showing signs and symptoms suggestive of acute or sub-acute pancreatitis.

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Cod Liver Oil Per Rectum as an Adjunct in the Treatment of Ulcerative Colitis*

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PATIENTS with ulcerative colitis not infrequently show marked symptomatic improvement under treatment—may, in fact, appear symptom-free—yet proctoscopic examination reveals that the mucosa of the rectum lacks sufficient healing power to arrive at complete regeneration or firm scar formation. Again, the process of healing may produce such a pronounced cicatricial formation that the rectum resembles a rigid fibrous tube. Some patients seem to lack the ability to respond either by symptomatic improvement or by local improvement of the rectal or colon wall. Such incidents are fully appreciated only by those who make visual examination of the rectum and lower sigmoid.

It is not the purpose of this paper to present a specific for the treatment of ulcerative colitis, but rather to present a measure which at times serves as a valuable adjunct to other forms of therapeutics. Two years' experience with cod liver oil has revealed some interesting findings. It is offered as an entirely new idea with some hesitation, for further scanning of the literature might reveal a suggestion or clinical report of its use. Up to the present, however, no such reference has been found.

Those of us who are more surgically minded about colon lesions realize that the immediate mortality in surgery of the colon for ulcerative colitis is high and that the later mortality is great enough to inspire search for a satisfactory non-operative method of treatment.

Since we have not arrived at definite conclusions regarding the etiology, we must apply those therapeutic measures which logic and experience have proved are valuable. Individualization of treatment and using the various methods of treatment with resourcefulness and good clinical judgment have accounted for those results which were successful.

An article by Lohr in 1934 on the local treatment of fresh wounds and burns with cod liver oil salve aroused considerable interest, and the use of cod liver oil per rectum seemed to the author to be worthy of careful clinical trial in ulcerative colitis. Lohr demonstrated that cod liver oil causes liquefaction of necrotic tissue, that it has a strikingly inhibiting effect on the bacterial flora of wounds and that it is a powerful stimulant of growth affecting all tissues. He is of the opinion that these effects are due to vitamins A and D.

Lohr also reported that ordinary streptococci, staphylococci and *B. coli* usually perish when placed in cod liver oil, probably from a lack of nourishment or from the surface tension of the oil. Lost and Kochergin report on 263 cases of ulcerated wounds treated with cod liver oil paste and believe their excellent results are

due to an abundance of the vitamins A. and D. They express the opinion that there is a lack of vitamins in pathologic lesions either because of an interrupted supply or an increased demand. As one considers the sequence of events in ulcerative colitis, this seems particularly applicable for the abnormal activity of the intestinal tract may inhibit proper absorption of the vitamins. Lost and Kochergin also state that cod liver oil lowers the vitality of pus-producing bacteria. Tumanskiy and Yatsevich found that the growth of streptococci ceases after one hour in both sterile and non-sterile cod liver oil and that staphylococci live but six hours. Hayashi concurs that the healing power of cod liver oil is due mainly to the effects of vitamins A and D and to the lipoids contained in the oil. It is generally agreed by most observers that vitamin A promotes tissue formation and that it is a physiologic prophylactic against infection by virtue of the fact that it maintains the health and integrity of the epithelial lining of the mucous tracts and skin. Vitamin D controls calcium equilibrium and regulates mineral metabolism. The report of the favorable use of calcium and parathyroid in ulcerative colitis by Haskel and Cantarow denotes the possible therapeutic value of vitamin D.

With these points in mind, it was felt that the application of cod liver oil directly to the diseased area in ulcerative colitis, rather than diluting it by passage through the stomach and intestines, was worthy of investigation. In order to better evaluate this treatment, it was first used on patients who had not responded satisfactorily to the various accepted therapeutic measures. These first three patients had been subjected to all known methods of treatment, yet they appeared to be fast approaching that stage where surgical intervention would be necessary. Two of them were still in the hospital and the third had been home but for a short time, and all energetic methods of treatment had been abandoned. They were merely on low-residue high-vitamin high-calorie diets, hot abdominal packs and paregoric and bismuth by mouth. Without otherwise changing the treatment, 4 ounces of cod liver oil were instilled into the rectum each day after a normal saline enema. After three weeks, the patients had not improved either symptomatically or in proctoscopic appearance. In view of the fact that slight temporary improvement had at times followed the routine use of yalren, acriflavine and gentian violet, it was decided to institute another such course of treatment and follow it immediately with cod liver oil rectal instillations.

Our experience with acriflavine has been similar to that of Crohn and Rosenak who reported in 1936 that of 75 cases treated, 44.5% were cured and 29.9% improved after a 2 to 4 year follow-up period. We have

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usually preceded acriflavine with yatren, however, and followed it with gentian violet for yatren is valuable in controlling any possible associated amebic infection, as well as for its general antiseptic qualities, while the selection of certain bacteria by acriflavine and of another group by gentian violet satisfies the hope that these drugs might be beneficial.

The method of treatment was as follows. Each drug was given by mouth and through rectal instillations for a period of five days. Yatren was used first, one tablet by mouth three times a day and at bedtime, with daily rectal instillations of 8 ounces of 1% solution, following a normal saline enema. This was followed with acriflavine, $\frac{1}{2}$ grain tablet three times daily and at bedtime, and instillations of 8 ounces of 1:5000 solution. The third period, gentian violet was given in the same manner as the acriflavine. As before, all these patients showed some improvement. Daily rectal instillations of 4 ounces of cod liver oil were begun immediately after the gentian violet treatments. Two patients improved markedly in three weeks, both symptomatically and by change in the appearance of the rectal mucosa, but because one was not making as rapid progress as the other, he was given a second course of the entire treatment. The third patient responded slowly, and was given three courses of the drugs, followed each time by three weeks of cod liver oil.

In each instance the bowel activity was reduced to four or five stools a day, the stools were more formed and were not accompanied by bleeding. The remarkable feature, however, was that immediately after starting the cod liver oil instillation, the ulcerated mucosa had a cleaner appearance, the necrotic grayish spots disappeared, and the granulating areas became bright red, with definite evidence of active epithelialization. The softer appearance of the bowel wall was unmistakable, the scarring did not produce as pronounced a contraction, and the epithelialization was smoother and more normal than that observed in previous ulcerative colitis cases. Of these three patients, two have remained symptom-free, with a quite natural appearing rectal mucosa, for 22 and 21 months respectively. The third patient, who did not respond so readily, has remained symptom-free except on two occasions when he contracted a little cold, which caused a mild flare-up of his symptoms. He has always responded quickly to a repetition of the treatment. X-rays reveal some rigidity of the colon in each case yet there is definite improvement over previous studies.

Fourteen other cases of ulcerative colitis have since been treated in a similar manner. None of these were of such a severe nature as the three mentioned above and only two had not received some form of treatment previously. These two have remained symptom-free for 8 and 14 months respectively, having no more than five stools daily and these of fairly formed consistency and not accompanied by bleeding. They are in good physical condition and are holding down positions. The other twelve victims had all had frequent recurrences of symptoms but had responded to various forms of therapy. Each was given one course of treatment with the dyes, followed by three to six weeks of cod liver oil instillations. It was deemed advisable to repeat one or more of the drugs occasionally, and for most of them the amount of cod liver

was reduced to 2 ounces. At times after two weeks of cod liver oil instillations, the oil was given only on alternate nights. Eleven of these patients showed more rapid symptomatic response, the mucous membranes appeared smoother and the intestinal wall less rigid than under previous treatment. The twelfth patient improved under the regime at first but after six weeks, it was concluded that no further benefit could be derived, although the mucosal wall did appear cleaner and healthier. Another form of treatment was instituted and recovery promptly followed.

Of these twelve patients, only three have had relapses severe enough to necessitate repetition of the entire course of treatment and the response has been most satisfactory in each instance. At the present time, the other nine have remained in excellent condition for periods of three to twenty months.

In but one instance did the cod liver oil act as an irritant and it was promptly discontinued. However, this patient, although she had formerly had frequent relapses, has not had a return of her symptoms in eight months following the cod liver oil instillations and has never felt as fully recovered. The rectal mucosa looks almost normal except for some excess mucus and a few hemorrhagic areas.

In two other cases, all symptoms have disappeared, yet the mucosa has not entirely healed, although it more nearly approaches normal than during previous remissions. Both have remained symptomatically well for some ten months.

The detailed technic of administering cod liver oil per rectum is as follows: An enema of one pint of normal saline is given first, and after this is expelled, two to four ounces of the oil are instilled with an all rubber rectal syringe while the patient is in the knee-chest position. This position is maintained for three to five minutes and the oil retained as long as possible.

Some vegetable mucin product or Kaomin is of value in obtaining better formed stools, as formed stools seem to have a beneficial psychic effect upon these patients. Since using cod liver oil as an adjunct in our treatment, we have had less difficulty in bringing patients to the stage where they have one or more formed stools each day. During the more active phase of the disease, a mixture of equal parts of paregoric and milk of bismuth is prescribed, two drams after each second bowel movement. The usual dietary restrictions and general supportative and symptomatic measures are mandatory.

SUMMARY

1. Cod liver oil instilled into the rectum is a definite aid to the healing of ulcerative colitis lesions.
2. It seems to be valuable merely as an adjunct and of no value if used alone.
3. Daily instillations of from two to four ounces have been used following a course of treatment with yatren, acriflavine and gentian violet.
4. Of seventeen cases treated, thirteen (76%) have remained practically symptom-free for periods varying from three to twenty-two months. Only two showed marked residual ulceration while being otherwise symptom-free. Several showed incomplete healing of a minor degree.
5. The chief value of the cod liver oil seems to be that it produces a cleaner, more pliable and healthier appearing bowel wall with less dense scar formation.

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The Relationship of the Diet to the Self-Regulatory Defense Mechanism

I. Hydrogen-Ion Concentration and Bacterial Flora

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INTRODUCTION

THE use of fresh fruit as premeals and as additions to the basal diet have been shown by many workers to influence the hydrogen-ion concentration, bacterial flora and the auto-regulatory defense mechanism of the gastro-intestinal tract. The variation encountered in fresh fruits gathered from different localities, and the still greater differences in fruits of different varieties and age prompted us to use a dehydrated apple powder of known composition.

Many factors have been suggested as the reason for the beneficial results obtained by the use of fresh fruit diets. Among these are the hydrogen-ion concentration and the carbohydrate (organic acids, cellulose, hemicellulose, lignin) content of the fruit. In dealing with the pH one must consider that a great variety of organic acids may be present in the fruit itself. Furthermore, other acids may be produced in the intestine by the action of body enzymes and of intestinal bacteria on carbohydrates, chief of which are lactic, acetic and butyric acids. Moreover some of these acids, aside from their effect on pH, may be toxic to certain organisms, thus preventing the development of a flora unfavorable to the host.

The experiments reported herein were performed in an effort to evaluate these factors and their relationship to the self-regulatory defense mechanism of the gastro-intestinal tract. By "the self-regulatory defense mechanism" we refer to the concept as developed by Arnold and his co-workers (1). Dehydrated apple was used in feeding because its stable composition allowed exact duplication of experiments. The data covers work done in determining the effect of the experimental diet on the fecal pH and the bacterial flora. Special attention was given to the study of the cellulose-splitting organisms since it has been shown that these bacteria produce organic acids. In experiments already reported (2), we studied the effect of vitamin A deficiency and uronic acid depletion in relationship to the lysozyme content of tissues and secretions. Our studies on the effect in vitro of various organic acid and pectin on intestinal organisms will appear in a subsequent report.

HISTORICAL

Bienstock (3) found that the upper half of the small intestine of laboratory animals as compared with the lower half was comparatively free of bacteria. Gessner (4) drew similar conclusions in his work with the human gastro-intestinal tract. To test the auto-sterilization mechanism, Schuetz (5) introduced B.

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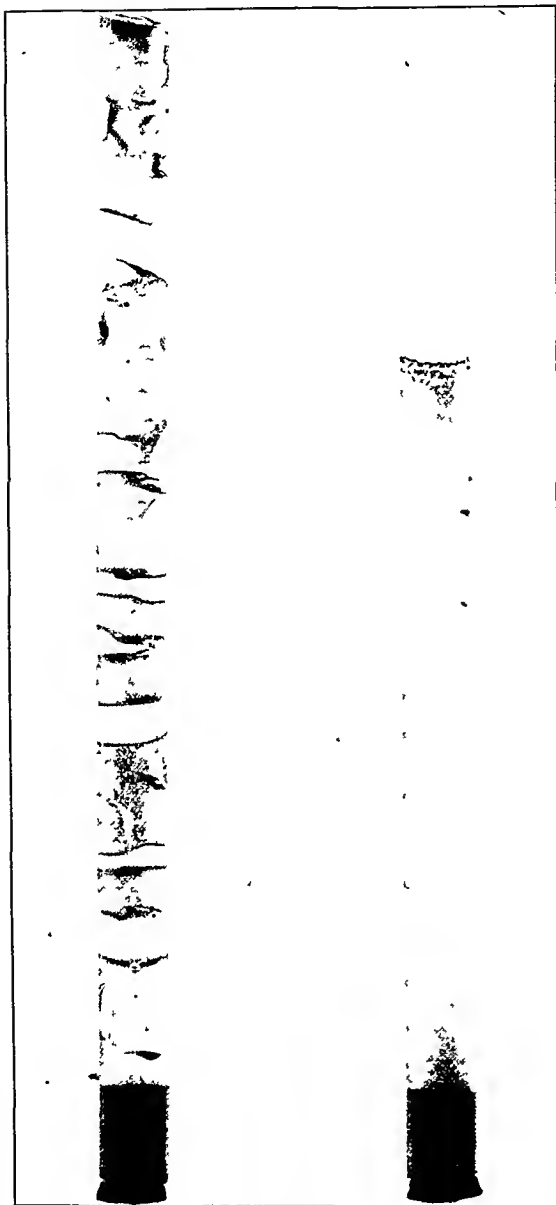


Plate 1. Veillon Tubes Cultures. I. Typical culture from cecum of pellet fed group showing 4 plus gas production. II. Typical culture from cecum of pellet plus apple powder fed group showing no gas production.

metschnikovi into the duodenum of dogs and found that the organisms were killed before reaching the ileum. Rolly and Liebermeister (6) substantiated Schuetz's findings, using *B. pyocyaneus* in rabbits. Van der Ries (7) concluded from his observations that the defense mechanism is one of auto-disinfection and not of auto-sterilization. Arnold (8, 9) investigated the effect of diet and meteorological changes on the endogenous enteric bacterial flora and the permeability of the intestinal wall. He found that in dogs, after the ingestion of an alkalinized food, a high-protein meal or

during the period of adjustment to a high external temperature or fever, there was a decided interference of the bacteriostatic power of the small intestine. In the small intestine, the interference with the bacteriostatic action on exogenous bacteria is accompanied by a marked disturbance in the regulation of the endogenous bacterial flora. The duodenum and upper part of the jejunum were the last to lose this auto-disinfecting power. The sudden alkalinization of the upper part of the small intestine and the presence of protein material or bile allows bacteria to pass through the wall of the intestinal tract and appear for a short period in the thoracic duct. Puppies kept in a hot room and fed *B. prodigiosus* in milk showed viable organisms in their stomachs. However, if the milk were acidified, no organisms were recovered.

Nedzel, Stonecipher and Arnold (10) administered saponin to dogs and studied the intestinal changes in the distribution of *Esch. coli* and in the hydrogen-ion concentration. Their results show that the oral ingestion of saponin caused a sudden change in the acid-base equilibrium and in the endogenous flora. This was associated with the appearance of viable *Esch. coli* in the organs of the animal. As the hydrogen-ion concentration increased, there was a decrease in viable *Esch. coli* in both the intestinal contents and in the organs. Nedzel and Arnold (11) and Johnson and Arnold (12) found that exogenous bacteria (*Esch. coli*) when introduced into the stomach in the presence of free hydrochloric acid lose their viability. When the gastric contents were alkalinized with a phosphate buffer solution, previously non-viable exogenous bacteria regained their viability. As the pH of the gastric contents increased there was a parallel increase in the viable exogenous organisms.

The above experiments were further extended by Johnson and Arnold (12). The test bacteria were suspended in saline, milk, phosphate buffer solutions and meat. At the beginning of the experiment there was an acid deficit which persisted for one hour. During this deficit, there were 150,000 bacteria per cubic centimeter. As soon as free acid was detected, no viable bacteria could be demonstrated. When alkaline phosphate solution was introduced to neutralize the free acid, viable organisms reappeared and persisted during the period of the acid deficit. They also found that if the gastric contents were removed when there was free acid present and then neutralized, no viable bacteria could be demonstrated.

Seidmon and Arnold (13) using rats as experimental animals, investigated the intestinal acid-base equilibrium and distribution of the bacterial flora on vitamin A and B deficient diets. The vitamin deficient rats were found to have a denser intestinal bacterial population and a more alkaline pH than the normal.

Recently a number of investigators have reported the use of fresh or dehydrated fruit either as a meal or as a premeal as a means of controlling the acid-base equilibrium in the intestine. Arnold (1), Bergeim, Hanzen and Arnold (14) and Esselen (15) using such fruits as apple, banana, cranberry, prunes etc. found that such diets tended to raise the hydrogen-ion concentration of the intestinal tract. With this rise, there was a decrease in viable *Esch. coli*.

EXPERIMENTAL

All of the rabbits used in this experiment were fed a basal diet of pellets containing ground oats, alfalfa

meal, ground barley, wheat germ meal, molasses, linseed oil meal, whole milk flakes, cod liver oil, ground wheat, soy-bean meal, brown malt, sprouts and minerals. Two experimental groups of animals were used.

tained finally that produced a tough membrane suitable for use. These membranes were treated with dilute NaOH to remove bacterial proteins. These membranes were then immersed in dilute HCl to remove

TABLE I -
pH determination of intestinal contents (glass electrode)

Group Fed Pellets						Group Fed Pellets Plus Dehydrated Apple					
Rabbit Number	Duodenum	Jejunum	Ileum	Cecum	Colon	Rabbit Number	Duodenum	Jejunum	Ileum	Cecum	Colon
N-1	7.05	8.28	8.38	6.27	6.83	A-1	6.98	6.80	6.00	5.47	6.75
N-2	7.11	7.74	7.80	6.55	7.01	A-2	7.01	6.59	6.27	5.98	6.11
N-3	7.10	7.41	7.77	6.90	6.99	A-3	7.08	7.04	6.58	6.59	6.18
N-4	7.19	7.60	8.25	6.46	7.71	A-4	6.92	5.86	6.01	5.61	6.78
N-5	7.14	7.61	7.05	6.00	7.12	A-5	6.49	5.98	6.00	5.50	7.11
N-6	7.22	7.69	7.04	6.72	7.10	A-6	6.80	5.87	6.11	6.48	6.05
Aver.	7.13	7.72	7.70	6.48	7.12	Aver.	6.88	6.35	6.14	5.60	6.32

both receiving the basal pellet diet. In addition one group received dehydrated apple (30 grams per animal per day). The animals were kept on these diets until all showed a substantial gain in weight. Growth curves of both groups were essentially the same. The animals were then sacrificed by a blow and the gastro-intestinal tract removed. The contents of five levels of the intestine, namely, the duodenum, jejunum, ileum, cecum and colon, were removed under aseptic conditions.

Nutrient agar and Endo's agar were inoculated from serial dilutions of the intestinal contents. From these plates, further identifications were made. Veillon tubes containing whey agar were also inoculated. After forty-eight hours incubation, these tubes were examined for gas production. Cultures for the determination of cellulose-splitting organisms were made on a modification of the media recently described by Aschner (16). The media described by Aschner is composed of membranes produced by the growth of *Acetobacter xylinum*. Cultures of *Acetobacter xylinum* were obtained from the American Type Culture Collection and from Dr. Aschner,* but suitable membranes from these cultures could not be grown. Cultures were made from material obtained from various stages in the manufacture of vinegar. One was ob-

tained finally that produced a tough membrane suitable for use. These membranes were treated with dilute NaOH to remove bacterial proteins. These membranes were then immersed in dilute HCl to remove

the alkali and then washed until free of acid. Aschner advised the use of wide mouthed bottles for the growth of these membranes. It was found, however, that the membranes could be grown more satisfactorily in petri dishes, thus providing membrane discs of the proper size. It was found further that Brewer's yeast could be substituted for marmite in the *Acetobacter xylinum* media and that maltose (three per cent) seemed to aid materially in the growth of these membranes.

Using the modified Aschner media, serial dilutions of the contents of the various intestinal levels were cultured. These cultures were made in duplicate and incubated under both aerobic and anaerobic conditions. The pH determinations of the five intestinal levels were made with a glass electrode pH meter. Direct smears were made of each level and stained by Grams method. Table I shows the hydrogen-ion concentration at the various levels. As will be noted the group receiving dehydrated apple showed a higher hydrogen-ion concentration in all five levels.

The greatest difference in pH was found in the ileum and the greatest hydrogen-ion concentration in the cecum. The pH values of the group receiving apple supplement showed a steady decrease in the small intestine. Just the opposite prevailed in the pellet-fed group. In both groups, the cecal pH was acid but in

*We wish to acknowledge with thanks the kindness of Dr. Aschner in providing us with a culture of the organism with which he worked.

TABLE IIa
Cultures of two intestinal levels

Rabbit Number	Group Fed Pellets				Group Fed Pellets Plus Dehydrated Apple			
	Cecum	Colon	Cecum	Colon	Cecum	Colon	Cecum	Colon
	Exch. coli %	L. Acidophilus %	Gram - Cocci %	Veillon Tubes Gas	Exch. coli %	L. Acidophilus %	Gram - Cocci %	Veillon Tubes Gas
N-1	83	6	11	+++	79	4	17	+++
N-2	80	4	16	+++	75	0	25	+++
N-3	91	0	9	+++	72	0	28	+++
N-4	57	2	11	+++	70	0	20	+++
N-5	83	3	14	+++	74	0	26	+++
N-6	79	2	12	+++	78	0	22	+++
Aver.	83.6	3.6	12.6	+++	74.6	0.6	24.8	+++

the former the acidity was almost ten times that of the latter. In the colon the pH tended to rise. In the pellet-fed group the pH changed to an alkaline one and equaled that found in the duodenum. The group getting the apple supplement still retained an acid re-

increase in the growth of cellulose splitting organisms in the rabbit—an herbivorous animal—it was thought that the rat might prove more suitable for demonstrating this point.

Two groups of rats were used. Both groups received

TABLE IIb
Cultures of two intestinal levels

Rabbit Number	Cecum				Colon			
	Esch. coli %	L. Acidophilus %	Gram + Cocci %	Veillon Tubes Gas	Esch. coli %	L. Acidophilus %	Gram + Cocci %	Veillon Tubes Gas
A-1	16	68	17	0	21	59	20	0
A-2	21	54	25	0	26	55	19	0
A-3	26	44	30	0	27	39	34	0
A-4	24	53	23	0	20	55	25	0
A-5	13	64	23	0	16	60	24	0
A-6	17	59	24	0	22	51	27	0
Aver.	19.3	57	23.7	0	22	53.1	24.9	0

action which was equal to that found in the jejunum. Cultures taken at these levels showed that the group receiving dehydrated apple developed an aciduric type of flora and that the Esch. coli were greatly decreased (Table II, a and b). Also the Veillon whey agar tubes gave gas production in the pellet-fed group while no gas was present in the cultures made from the dehydrated apple group (Plate I). As the cecum and colon were the only two levels giving satisfactory cultures, these only were reported.

In order to determine the number of cellulose splitting organisms present, cultures on the cellulose membranes were made from the cecum and colon of both groups. It was thought that the group receiving dehydrated apple might show an increase in cellulose splitting organisms due to the presence of hemicellulose and pectin. Serial dilutions were made and incubated under aerobic and anaerobic conditions. It was found that the dietary supplement made no difference in the number of cellulose splitters. The anaerobic plates, however, both groups showed many more colonies than the aerobic. Table III shows the result of the cellulose cultures given in the number of organisms per gram of fecal contents. Since the feeding of dehydrated apple as a source of cellulose did not cause an

a vitamin A free diet plus cod liver oil. In addition, the food of one group was supplemented with dehydrated apple (25 per cent). One animal from each group was sacrificed at ten-day intervals and cultures of the intestinal contents were placed on the modified Aschner media. The last animals sacrificed had been on the diet 42 days. All cultures were made in duplicate and incubated under aerobic and anaerobic conditions. No difference in the number of cellulose-splitting organisms could be detected in the two groups. It is hardly to be expected that the addition of apple to the diet of an herbivorous animal would result in any material change in the number of cellulose-splitting organisms. Alteration in the fecal flora of the rat, however, is to be expected. That it did not occur may be due to a failure to extend the feeding over a long enough period of time.

DISCUSSION

Many years ago, Metchnikov advocated the use of buttermilk. He claimed that the establishment of an aciduric flora in the intestine was of value in that it tended to supplant putrefactive organisms which are capable of producing toxic and irritating materials.

More recently the apple has been advocated as a valuable adjunct to the diet. Clinically, such additions were found to be beneficial although reasons for this were not definitely known. The data submitted in this report show that this food substance is capable of bringing about many if not all of the same changes in the reaction of the intestine and in the intestinal flora as were claimed by Metchnikov for buttermilk. Evidence is increasing to the effect that certain food substances such as cellulose, hemicellulose and perhaps pectin to some extent, can be broken down in the intestine with the liberation of certain organic acids which may have a specific bactericidal or bacteriostatic value. The most important of these acids are claimed to be acetic, lactic and butyric.

Any dietary regime which results in changing the intestinal reaction to one favorable to the growth of the aciduric type of organisms and detrimental to the development of putrefactive processes should be favor-

TABLE III
Cellulose-splitting organisms from cecum (organisms per gm.)

Pellet Fed Group			Pellet + Apple Fed Group		
Rabbit	Aerobic	Anaerobic	Rabbit	Aerobic	Anaerobic
N-1	4,000	120,000	A-1	5,100	217,000
N-2	2,100	200,000	A-2	4,400	146,000
N-3	3,500	180,000	A-3	2,100	170,000
N-4	4,900	223,000	A-4	3,800	121,000
N-5	1,900	261,000	A-5	5,400	240,000
N-6	3,300	192,000	A-6	4,800	190,000
Aver.	3,280	194,300	Aver.	4,250	180,600

ably regarded. Furthermore, more importance from a dietetic standpoint should be given those foods whose residues in the intestine can give rise to substances inhibitory to gas production.

CONCLUSION

The addition of dehydrated apple to the diet of the rabbit gives results similar to those obtained by other workers using fruit. The animals receiving apple had

an increased hydrogen-ion concentration in the intestinal contents. The intestinal flora was changed from one in which *Esch. coli* predominated to one in which the acidophilic type of organism was dominant. Furthermore, the number of gas-producing organisms was considerably reduced. The addition of apple to the diet of both rabbits and rats for a period of 42 days did not alter the cellulose splitting flora of either of these groups.

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Health and Nutrition of High Andean Indians

By

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STUDIES of the dietary habits of primitive races in relation to their physique, longevity and health status have contributed much to our present day knowledge of nutrition. Notable among these are McCarrison's nutritional researches among the Hunzans in Tibet, Stefansson's observations on the dietary of the Eskimo, Escudero's study of the eating habits of the gauchos of Argentine Pampas, and Metchnikoff's deductions from a study of the Bulgarian peasant dietary.

It was my privilege during the summer of 1937 to study at first hand the eating and hygienic habits of the Indians of the Lake Titicaca basin in Peru and Bolivia. Inasmuch as very little seems to have been written about these people from a medical standpoint it seems justifiable to record some of my observations and deductions concerning their nutrition and the diseases from which they suffer. I am greatly indebted to Dr. Abilardo Ibanez, General Director of Military Sanitation of Bolivia, Dr. Frank S. Beck, of the American Clinic at La Pas and Dr. James V. Price, Chief Surgeon at the Cerro de Pasco Mines for many years, for much of the information contained in this paper.

The Indians, one of the chief ethnical elements of the Bolivian nation, are called AYMARAS. They occupy the Andean plateau extending from southern Peru and take in the shore and islands of Lake Titicaca and extend as far south on this plateau as Auro.

A discussion of the climate of the Lake Titicaca basin is of fundamental importance in a consideration

of the health status of its inhabitants. The lofty plateau, called Calloa, containing the lake basin, has an elevation of a little over 14,000 feet, about the height of our Pike's Peak. Its nearest boundary is about 11° from the equator. The climate is severe, even in summer when there are biting winds, and in the winter when the plateau is swept by violent gales and hailstorms. In the winter the temperature goes a little below freezing, but in the direct sunshine it is almost hot. There is about 20° difference between the day and night temperature. The snow capped mountain ranges, 75 miles in length, may be seen less than 100 miles away from the center of the lake. Lake Titicaca never freezes over, though ice may form in the shallow water. The rainfall is less than 10 inches.

The soil is sandy, but fertile, as evidenced by the luxurious gardens around the watering tanks along the railroad. On the banks of the lake there are terraced garden plots but the variety of the crops is limited to a few hardy plants including the potato (which originated here). No manure or other fertilizer is used and the land is allowed to lie fallow for periods. After so many hundreds of years of cultivation, without fertilizer, the land must have had its mineral content tremendously reduced, with resulting low mineral salt content of its food products. The vitamin content must also be low.

The Aymara Indian is small of stature, being a little taller than the Labrador Eskimo but a trifle shorter than the Japanese, averaging about 5 ft. 4 in. He has a well developed chest, small bony framework,

with muscular arms and calves. The feet are small in spite of his barefoot habits. The head is large with wide, high cheekbones like the American Indian. The neck is thick, the nose large, lips full and eyes small.

The intelligence of the Andean Indians developed greatly under the Inca rule. They became obedient, industrious and thrifty, but these good habits were transformed by the cruelties inflicted upon them by their conquerors. In addition to being exploited and being normally melancholic and handicapped by bad food, bad housing and year-around cold, they have become sulky creatures and the impression one gets is not a favorable one. They laugh, it seems, only when they are drunk. They are dominated at all times by whites and half-castes, public officials, priests and sorcerers. They have many good qualities, being frugal, submissive and docile when kindly treated. The women are never idle, even at rest you see them making yarn with their crudely made distaffs. They make most of the family's clothing.

Their hair is thick, black and straight. Beards are rarely seen. One observes a few hairs on the upper lip, but nothing which one could dignify with the name "moustache". Inquiries brought out the interesting fact that grey hair is a rarity among men and women, no matter how old. The hair rarely falls out and baldness is extremely uncommon in spite of the prevalence of syphilis. Contrary to some medical opinion as to the effect of hat wearing in producing baldness, the Andean Indian wears a hat almost from the day he walks. It is pulled down tightly on his head because of prevailing winds, and shields the scalp from the sun's rays. Both of these effects, circulatory constriction and obstruction of actinic rays should, theoretically interfere with hair growth, but such is not the case.

A study of the teeth brings out certain points of nutritional interest. In general the babies' dentition is delayed about six months longer than the civilized child. They nurse until about the eleventh month. Children after weaning get very little milk as it is quite scarce. There are very few goats in Bolivia and their milk is not used as food. Llama milk likewise is not used. Cows are now becoming more numerous and their milk is gradually being added to the diet. An interesting point with reference to sanitation and cow "psychology" is that the calf sucks at the same time the cow is being milked.

At fourteen, teeth are frequently absent due to dietary deficiencies. This is noted in the Indians living near railroads where civilized food is obtainable. Those living near a sugar plantation have a great deal of dental caries, which seems to confirm the commonly accepted belief that an excess of sugar hastens tooth decay. It is my opinion, however, that the sugar itself is not so much the direct cause of decay as is the replacement of other important vitamin and mineral salt containing food by sugar. The third molars erupt late or not at all. Anomalies of the teeth are rarely seen. At the age of twenty any teeth which have survived the ravages of caries are about level with the gum margins as the result of chewing very hard shelled beans.

The Andean zone of Peru and Bolivia contains a population of about 8,000,000, most of whom are Indians. The Indian population has been stationary for the past two or three hundred years. Large families

are rarely seen, the average being less than four. Over 25 per cent of the marriages are childless.

Infant mortality is appalling. It is not unusual for a woman to have had a dozen pregnancies with but one living child. Dr. Price told me of one woman, who had had twenty children with but one living. Dr. Beck informed me that of 2,500 recorded births 1,600 died before they were one year old, and of these 25 percent died of whooping cough, a disease which seems particularly devastating among these people.

Parental love seems to be of a very indifferent type. As an example, I may mention the case of a gardener who did not appear for work one day. When asked the following morning the reason for his absence he cheerfully replied that his three year old child had died. His employer, after expressing his sympathy, was shocked by the gardener's reply: "Good luck for me, one less mouth to feed."

Abortions are very common. The Indian women often accomplish this by pounding on their abdomens. Midwives function here in a very primitive manner and produce abortions by inserting foreign bodies. Should the mother not succeed in aborting the unwelcome child she may dispose of this child after birth in the following manner. An infusion of the shells of the native peanut is given the infant. This acts as a slow poison. The infant succumbs in two or three days. Dr. Beck tells me that when such a mother resides in the neighborhood of a clinic or a missionary physician she will bring the baby to the clinic doctor after it has been given the poisoned infusion. The doctor examines the baby, notes that it is ill and prescribes for it. The following day the mother reports to the doctor that the baby has died and asks for a death certificate. The doctors are now aware of this method of infanticide and acquaint the civil authorities whenever a case looks suspicious.

The life of these Indians is severe and hard in the extreme, though they are never faced with actual starvation. The diet consists practically of meat, potatoes, corn (mote), very few vegetables and very little butter, sugar, fruit or milk. They eat when they are hungry, hence meal periods are irregular except for those working in mines or other "civilized" jobs. They are small eaters and according to Dr. Ibanez average about 800 calories daily. Gorging is therefore, confined to feast days.

The potato, in the form of chuno, is the mainstay of their diet. The crop is harvested about June first, spread out and covered with straw and allowed to freeze for several days. The potatoes are then intermittently exposed to the sun which causes the water to exude, and to frost. They are turned repeatedly and soon shrivel up. Then they are mashed, leaving a substance similar to coarse starch. This farina-like material is then stored in tightly closed skins. It can be kept indefinitely and throughout the year is the major item in their diet. Oca, a kind of sorrel, quiona, and edible chenopodium, and a specie of millet are used to make soup. Everything is strongly peppered. On account of the poor cooking facilities very little extremely hot food is taken. Chalona, lamb's flesh dried in the sun, and sometimes the flesh of the llama is used. In the lake region, fish, mostly carp, enters quite largely into the diet.

The endurance and speed of these Indians is amazing. The men carry a load of 60 to 80 pounds from 20

to 30 miles without apparent fatigue. When they do not carry a burden they can cover 50 miles a day for several consecutive days.

The houses are made of mud which is baked firmly in the sun. Practically no furniture is used, the bed consisting of a slightly elevated mud platform, over which dirty rags and skins are spread. In all my travels I have never encountered such personal filth. Hygienic conditions are deplorable, entire families being crowded in a gloomy, crowded, filthy hut. Indian servants of the white Bolivians in the Lake Titicaca region are treated almost on a par with dogs. They sleep in some dirty corner of the house and are fed on scraps. The squatting position which is assumed widely is a protective measure serving to keep them warm by covering the lower extremities. Small fires are made of llama dung, bits of dried grass or roots over which food is cooked. The natives do not seem to feel cold at all, although I stood about clad in woolen socks, muffler and heavy suit and overcoat. They walk barefooted in the heaviest frosts or may wear sandals made of skin, but rarely are stockings worn. I saw Indian women standing in the shallow waters of Lake Titicaca, for an hour at a time, when there was ice along the shores.

Bathing is never indulged in as the water is too cold and there are no facilities for heating it. Clothes are only removed when they wear out. The women put on a skirt at an early age and as this one becomes worn another one is put on over it, so that frequently you see a woman of twenty years of age who is wearing a dozen or more skirts. They sleep in their clothes to give themselves added warmth at night. When windward of one of these women a sickening ammoniacal odor gives mute olfactory testimony of their presence. The exposed parts of their bodies, face, feet and hands always appear dirty. Body lice and head lice are very common. Bed bugs are not found in the highlands but are a pest in the lowlands, as every tourist will attest.

These Indians drink very little water and appear to be in a state of chronic dehydration. Constipation, in spite of their meager diet and the use of coca (cocaine) does not appear to be a racial characteristic. This may be explained possibly by their active lives, the absence of chairs, and the habit of squatting while resting. It is a ritual, at the end of each day, to wander from their huts and spend at least fifteen minutes in the squatting position for the purpose of elimination. No log, limb or other support interferes with intra-abdominal pressure.

Since the Chaco War, tuberculosis, particularly of the bones and glands has become very common among them. When they went to the low Chaco country and lived under abnormal dietary and climatic conditions the toll from tuberculosis was tremendous, vastly more dying from it than from lead and steel. Those who survived carried the disease back to the highlands where, on account of unsanitary conditions and nutritional inadequacies, it spread rapidly.

Pneumonia is fairly common and while usually fatal to whites, the mortality among the natives, from the data obtainable, does not appear to exceed civilized statistics. Bronchitis is common. Colds are frequent though sinus infection is not frequently diagnosed. Hay fever, apparently, does not exist. Asthma is a rarity, due possibly to the scant vegetation, rarified air or low streptococcal virulence.

Skin lesions are common. Large ulcers of the shins, forearms and cheeks are frequently seen, due to a form of Leishmaniasis. Treatment consists of intravenous injections of tartar-emet, except when there is involvement of the liver and lungs. A very contagious form of pustular dermatitis, probably impetigo contagiosum, is common and is frequently seen on the face and often covers the entire body. All the other contagious diseases of childhood are found frequently and are similar to those observed in this country. Carbuncles are common, particularly on the neck.

Arthritis of all types is conspicuously absent in the highlands, but, according to my advisors, is quite common in the lowlands. This came as a surprise to me considering their deficient dietary, and cold, damp indoor and outdoor climate in which they live. This might be of interest from the standpoint of that bogey of rheumatology, "metabolic" arthritis. The absence of gonorrhoeal arthritis, atrophic arthritis and streptococcal diseases suggests low pathogenicity of streptococci at high altitudes.

Cancer of the gastro-intestinal tract or skin is rarely seen. Cancer of the uterus is just about as common as among civilized women. Contrary to the prevalent belief about the physical fitness of primitive women, gynecological pathology is about as common, abnormal births as frequent and labor and post-delivery convalescence about as long as that of civilized women.

There is a great deal of typhoid fever among both the Indian and whites. Ulcerative colitis was never seen among the Indians and rarely among the whites. Mucus colitis was occasionally seen. Amoebic dysentery does not exist in the higher altitudes. Typhus fever is very common. Tetanus has not been seen at the American Clinic at La Pas for 10 years. Anti-tetanus treatment is never given.

Dr. Beck told me that it is a safe estimate to conclude that 40 or 50 per cent of the Indian population has syphilis. Tertiary syphilis is never seen among the highland Indians. This fact has, of course, been noted among other primitive people, but it appears that the highland Indian is particularly immune to the tertiary form. This fact offers an interesting field for speculation because his life span favors the tertiary stage. Are genetic, climatic or barometric factors responsible for this changed host-parasite relationship?

High blood pressure is uncommon. Endocarditis and septicaemia are rare. Coronary disease is definitely less common among both the whites and Indians, due undoubtedly to more simple living and less worry and haste.

Those who survive 20 years of age stand about the same chance of living to be 60 as do civilized persons. The men and women at 40 often look 60.

Cataracts are very common. Blindness of venereal origin is prevalent. According to Dr. Beck no basal metabolism studies have been made in Bolivia. Hyperthyroidism occurs only occasionally. Simple goiters are not observed at high altitudes but are common in valleys below 10,000 feet.

Diabetes is rare among clinic cases. Rickets is not observed to the degree or with the frequency that one would expect. Gall bladder diseases are infrequent among hospital cases and no case of cholelithiasis has been found at the American Clinic. Cirrhosis is but rarely seen. Cases of jaundice are extremely rare.

Nephritis is uncommon. No kidney stones have been noted, in spite of habitual dehydration and low vitamin A intake.

Cocaine, (derived from the chewing of coca leaves) and not food is their first necessity of life. They carry a little bag of coca leaves as well as a little pouch containing a mixture of lime and wood ash. It is interesting to note that their ancestors hundreds of years ago empirically discovered that the alkaloid cocaine could be extracted from the leaves in an alkaline medium. The technic is to mix a few crushed coca leaves with a few pinches of wood ash and lime making a quid which they use as we use chewing tobacco. One rarely sees an Indian without a bulging cheek. The leaf itself I found practically tasteless. I chewed the mixture for 15 minutes and felt no immediate feeling of euphoria though I did note a definite loss of appetite at the next meal period. The coca does not produce accumulative effects in the manner in which the Indians use it, though it undoubtedly has contributed greatly to the dullness of intellect which seems to characterize them. Its effect is apparently twofold. It seems to be moderately stimulating, thus making up for the depressing effect of a low blood sugar, which must result from their low caloric diet. Likewise, it unquestionably inhibits gastric secretory and motor function besides dulling hunger sensations. I inquired of the three physicians interviewed about the effect of the coca habit on the gastro-intestinal tracts. According to their observations the habit, even in habitues of long standing, produces no pathological condition. The effect seems to be conditioned by altitude and climate, and appears to play a compensatory role in a biochemical adjustment to high altitude. They rarely reach a toxic stage and it appears that tolerance is not established, as they continue to take the same dose over a period of years. As is well known, cocaine, first stimulates, then produces hallucinations followed by signs of mental and moral laxity. Unlike the taking of opium it can be stopped at once without withdrawal symptoms. While chewing coca leaves Indians can undergo great exertion, and work intensively for long periods of time without apparent fatigue and with very little food. Dr. Ibanez told me that he is convinced that the coca leaf supplies considerable vitamin C. Is it not reasonable to think that the lime and wood ash minerals play an important role in correcting the deficient mineral intake?

Alcoholism ranks with coca leaf chewing as a major vice among these people. It is quite evident, judging from experience with our native Indian and his "fire-water" that the brown race cannot drink with moderation. The Andean Indian does his "two-handed" drinking on holidays. But inasmuch as holidays and work-days seem about evenly divided, he is, for all practical purposes, in a mild state of chronic alcoholism. His favorite drink is white man's alcohol, which he usually dilutes with an equal part of water. He seems to have an extraordinary capacity for oxidizing alcohol, as it is not uncommon to drink several bottles of rum on special feast days. All financial surpluses above bare living wants go for the purchase of alcohol in one form or another. They drink Chicha made from maize which is allowed to germinate. Water is then added followed again by alternate drying and moistening, after which the mash is baked. Water is then added and fermentation takes place. This is called their

"luxury beer". It has twice the alcoholic content of our own beer, and is quite pleasant even to the civilized taste. Another drink which I am frank to say, I did not sample, which is called Chicha-mascada is made as follows. The old folks who are too feeble to work, spend their hours of leisure in chewing maize and expectorating the resulting mixture into a common bowl. This "salivary" concoction is then allowed to ferment, resulting in a drink of high alcoholic content. After mentally analyzing the biochemistry of this beverage, it suddenly dawned upon me that in view of the prolific and protean flora and fauna in the mouths of these Indians an alcoholic extract of these organisms might result in a vaccine incorporated in the beverage. One cannot help but conclude that the Andean Indian's love of drink is due to the neutralizing effect of alcohol upon the secondary depressive effects of chronic cocaine poisoning.

It is exceedingly interesting and instructive to study the medical practices of the early Incas, and that of their descendants of today. The physician in those early days was apparently a man of high moral character and greatly respected. Judging by ceramic evidence and from the numerous trephined skulls exhibited in the Lima Museum, the ancient Peruvian surgeons operated on the skull frequently. It has been estimated that about 2 per cent of the population was trephined. Epilepsy was apparently a major indication and though uncommon today, was quite prevalent at that time as a result of depressive fractures and wounds inflicted by clubs and stone slings. A sharp instrument made of obsidian, a hard black glass, a product of volcanic action, was their favorite implement. The patient before being trephined chewed coca leaves which produced a mild general anaesthesia. During the operation the area was bathed in an infusion of red willow bark which apparently has some antiseptic power. Mashed coca leaves were also applied to the wound to deaden the pain. The wounds were usually dressed with hot oil over which was placed cotton fiber, derived from a plant which was indigenous to Peru. Blood letting was a common practice even though they did not understand the anatomy of the veins. The lancet made of sharp pointed flint was inserted in the vein nearest the point of pain. Cupping was also used by these ingenious peoples. They cut off the end of a cocanut shell and produced a vacuum with it. The Indians today practice the custom of piercing the temporal artery with a sharp piece of glass. This type of bleeding is commonly used.

The Inca pharmacopoeia included the Chillcha herb, used for the relief of pain in the joints; Mamasa leaves, as an astringent, finely powdered tobacco for colds or bronchial conditions; the bark of the Malle tree for healing; a purge made from roots; glandular extract made from the rooster; and of course, cocaine. As diuretic they use an infusion made from corn silk, which seems to be as effective as some of our more refined diuretics. The Aymaras Indians use about one hundred different herbs, which should provide an interesting pharmacological study.

The Collaquayas, Bolivian medicine men who travel up and down the Andes practicing all kinds of strange medical customs, apparently have a certain kind of medical and botanical knowledge, which has come down through the generations. Some of the herbs which they use have been shown to possess therapeutic prop-

erties. These Indians travel all over South America giving treatment with an assortment of seeds, resins, plants, roots and leaves. As their supply gives out they replace them with substitutes. It is quite apparent that autosuggestion plays a definite role in their armamentarium.

Considering the climate and hard struggle for existence and the small number of products of the soil it is rather strange that human beings should continue to live in so inhospitable a land when it is but a few days journey by foot to the East whose hot valleys and abundant vegetation afford vastly easier conditions of living. In spite of the civilized surroundings which have crept into their midst the high Andean Indians present racial characteristics today very similar to those existing before the Conquest. We, therefore, have for our study a great population of primitive people who have lived $2\frac{1}{2}$ miles above sea-level, under unfavorable circumstances and cruel exploitation for over 400 years. Yet in spite of all this they are more advanced in the arts of life than their neighbors who live lives of ease in the tropics.

The following comments by Huntington in his book, "Climate and Health", may condone some of the shortcomings of these Indians.

"If immigrants possessed of an unusually high inheritance, either by reasons of strenuous natural selection or by actual biological mutations, should come to such a region, the relatively stimulating quality of the climate would combine with their innate ability to enable them speedily to dominate the indigenous population, and to develop many new ideas. Yet we should not expect such a civilization to endure so long

or rise so high as those in more favored regions. The people would tend to exhaust themselves for they would never experience any restful changes of seasons, and would be stimulated at all times. The most nervous people would die out partly because they would exert themselves too strenuously, and partly because nervousness is a potent agency in reducing the birthrate. Self-control would also be weakened, thus leading to vice and excesses of various kinds. In various other ways such a climate as that of Peru would be stimulating for a while, but would lead to exhaustion sooner than would one where greater variability prevails."

We must, therefore, be generous in our appraisal of the high Andean Indian. Though they are not likable in character, we must remember that cold, high altitude, meager food, subjugation, exploitation, disease, cocaine and alcohol poisoning have made them surly, cruel, pugnacious, uncooperative and fanatical. It is my belief that kindness, improved environmental conditions, proper medical care and intelligent educational and religious training would entirely change the character of these people and make them into a peaceful, sober, healthy race which would soon lift Bolivia out of its doldrums. When one realizes how much the great mining companies owe to the Indian, without whose special physical aptitudes mines could not have been successfully operated, it seems only logical that the mine owners and their governments should give constructive thought to the welfare of these people. A hospital ship on Lake Titicaca, which has a shore line of nearly 400 miles, would bring them inestimable health benefits.

Editorials

HUNGER, APPETITE AND THIRST

THE physician is often much concerned over the inability or unwillingness of a particular patient or child to eat, and sometimes he turns to the physiologist for some hint or explanation. Unfortunately, the physiologist cannot as yet help much, but, as will be seen from what follows, he has been doing some thinking on the subject.

Hunger is doubtless made up of several components, and some persons experience one type of sensation and others another. Besides sensations referred to the epigastrium, there are feelings of weakness and a desire for food.

Some authorities believe that hunger is produced by contractions of the stomach or the bowel; others that it is due to a group of sensations reaching the brain from many parts of the body; others that it is due to a lowering of food supplies in the blood, and others, that it is due to changes in the brain.

Contractions of the empty digestive tract are not the sole cause of the hunger sensations. Patients have continued to experience hunger after complete or partial gastrectomy. Distention of the stomach with non-nutritious material may relieve for a short time the epigastric discomfort but not the hunger. That

emptiness of the stomach is not essential in producing hunger is shown by the fact that patients with pyloric obstruction and a full stomach will still get hungry. Rabbits also get hungry although their stomach is never empty. Furthermore, hunger does not come simply because the stomach has emptied; it does not come necessarily after hours of fasting. Many persons are not hungry in the morning after the longest fast of the day. Curiously, the taking of black coffee or a sedative, or the smoking of a pipe, may for a time relieve hunger.

People get hungry for certain specific foods. The stout woman on a reduction diet, with her stomach filled with salads and vegetables, may still be ravenously hungry for a pork chop. People compelled for a time to eat fish may remain hungry for beef. Rats on deficient diets are hungry for the foods that they need to supplement the feeding. That mere eating does not satisfy hunger is shown by the fact that a dog with an esophageal fistula when "sham fed" keeps gulping food for long periods of time.

Part of the sensation of hunger is doubtless due to the lowering of the body's stores of food in blood and liver. The patient with exophthalmic goiter and a fast metabolic rate is likely to be abnormally hungry,

but the man whose fast metabolic rate is due to fever is not hungry.

The diabetic is hungry in spite of the fact that his blood is full of sugar, and the obese are very hungry in spite of a normal metabolic rate and large bodily stores of food. Perhaps their trouble is that they inherit a peculiarly sensitive hunger mechanism. The pregnant woman is often hungry, as she should be with her increased need for food.

The very thin, who should be hungry, usually are not. Hunger does not increase steadily during fasting but *commonly lets up on the third day*. That hunger is not due in most part to the need for replenishing the body's stores of food is shown by the fact that in many patients the sensation disappears as soon as a few mouthfuls of food are eaten.

In normal persons the level of the blood sugar does not always influence hunger. The intravenous injection of glucose, however, can stop hunger in dogs and men. The injection of emulsified fat into the blood of dogs does not appease hunger. In man and dogs jejunal feeding regularly relieves hunger in some individuals and not in others. Wherein lies the difference no one knows. After vagotomy such feeding is not so likely to appease hunger, but after section of both the vagus and splanchnic nerves animals continue to desire food. In dogs, distention of a Vella segment, cut away from the rest of the small bowel, will take away all the dog's interest in food.

Hunger can arise from a diseased brain, as in cases of bulimia. Hunger can be removed by an inadequate diet and it can be restored sometimes by giving vitamins or an adequate diet. Sailors will continue to eat and digest even when constantly seasick.

Appetite appears to be different from hunger. It causes people to go on eating after hunger has been appeased. There is a large psychic component. Hungry persons may refuse to eat because of lack of appetite for the food presented. Animals have a sixth sense which shows them what they need to eat to balance the diet and avoid illness.

Thirst has been thought to be due to dryness of the pharyngeal and esophageal membranes, but this is not the essential factor. Thirst can be produced by injecting intravenously hypertonic solutions of salts, and after dehydration of the body it can be relieved by the injection of physiologic saline solution. In diabetes insipidus the primary trouble appears to be an increase in thirst. If an excess of water is not taken there is no polyuria, and if polyuria is prevented, polydipsia remains.

Recent studies have shown that the amount of water drunk by a thirsty animal is exactly what is required for its metabolic needs. Other studies show that the amount of water needed is correlated closely with the surface area of the body.

Walter C. Alvarez, Rochester.

THE STRANGE ABILITY OF ANIMALS TO CHOOSE A BALANCED DIET

ONE of the most remarkable and as yet unexplained faculties of animals is their ability to recognize and pick out not only the foods which they need to supplement a defective diet, but also foods which are doing them harm. Years ago I was much impressed when McCollum told me of the difficulties the early experimenters had before they realized that rats, when

given a mixture of foods, would to their advantage pick out certain substances and reject others. In the early days of dietetic research this explained some of the discrepancies in the results of different workers because some had mixed and pulverized the food while others had not. Later it became customary to supply all food in a mixture ground so fine that it was impossible for the animals to choose or reject any particular set of particles.

A few years ago I was astonished again when Franke, in the South Dakota Experiment Station, told me that his rats would, within a few days, recognize the fact that wheat, containing perhaps 7 parts in 1,000,000 of selenium, was causing their ill health. If then allowed to choose between two samples of wheat, one normal and the other containing the poison, they would reject the latter, and, if supplied only with selenium-containing wheat, would go hungry rather than touch it.

It is curious that a rat should have a faculty which is not possessed to any great extent by adult man. As every allergist knows, there are thousands of men and women in the United States today who go on suffering miseries of many kinds without ever suspecting that these are due to the eating of one or more of the commonly used foods. More curious yet is the fact that infants and children seem often to sense the harmfulness to them of certain foods, such as milk, which they then valiantly refuse to touch. This was once thought to be due to simple stubbornness and natural cussedness, but today every allergist pricks up his ears on hearing of these dislikes because often they point to the fact that, in infancy, the milk did much harm and the child sensed in some unknown way something which was not suspected by his mother or perhaps even by his physician.

That these sensitivenesses can be recognized even in infancy was shown recently by the experience of some friends of mine. When their child was a few months old, he was started on the usual feedings of orange juice. For a few days he took it with great delight, but then he began to bloat and to have abdominal pain. Before his parents and the pediatrician could be sure that the orange juice was responsible for this turn of events, the baby had made his diagnosis and had expressed strongly his determination to swallow no more of the allergen. Actually he was right, and when the feedings of fruit juice were stopped he was comfortable again.

In a recent paper, Richter, Holt and Barelare (Am. Jour. Physiol., 122:734-744, 1938) report their studies of the way in which rats will select their diet when given a chance to do so. Actually the animals were found to be good at picking out a balanced diet with all the necessary vitamins and nutritional substances. Apparently they have a special appetite, not only for salt and sugar, but for protein, carbohydrate, sodium, calcium, phosphorus, potassium, and the vitamins!

It will doubtless be somewhat of a blow to many persons to realize that a rat has in some ways more sense than has homo sapiens!

W. C. A.

A NEW TECHNIC FOR THE STUDY OF IMMUNOLOGIC AND ALLERGIC REACTIONS

A NEW and most interesting method of approach to the problems of immunology and allergy has been made by Shaffer and Dingle (Proc. Soc. Exper. Biol.

and Med., 38:528-530, 1938). These men took advantage of the marvelous new methods which have recently been developed by Langmuir and his coworkers for the adsorption of substances onto the surface of suitable plates with the formation of extremely thin monomolecular layers. In these layers the molecules will all be arranged in the same way, with perhaps a long chain toward the plate and a short chain toward the air. The thickness of the film can easily be measured with the help of suitable optical technics, and the several properties of the molecules and the ways in which they combine with other substances can be studied as never before was possible.

Shaffer and Dingle have been making such a layer with a stearate molecule and then studying the ways in which solutions under investigation are adsorbed onto the layer. For instance, a 2 per cent solution of crystalline egg albumin, when applied to the surface of stearate, wetted it readily and there was an increase in thickness of approximately 40 ångströms. Some anti-ovalbumin rabbit serum applied to the albuminized area combined with the antigen and increased the thickness by 100 ångströms. That the reaction was a specific one between antigen and antibody was indicated by the fact that no adherence could be obtained

between antiserum and the stearate surface or between normal rabbit or horse serums or heterologous immune serums and the monolayer of antigen.

Interesting was the discovery that on attempting to deposit a second layer of egg albumin on the upper surface of the anti-ovalbumin antibody already adherent to a base of albumin, the albumin solution removed the antibody, leaving attached to the stearate surface only the original albumin layer. This experiment not only shows an analogy to the effect sometimes observed when an excess of antigen is added to an already existing immune serum-antigen complex, but also may indicate the relative forces existing between antigen and antibody as compared with those which bind albumin to stearate.

Interesting observations were made also on the reactions between certain antipneumococcus serums and pneumococcus carbohydrate from the corresponding type of organism.

There is no telling what advances will come from the use of this most ingenious and remarkable technic, but there should be many. There is nothing so important in science as the discovery of a new technic which opens up a new field for research.

Book Reviews

Clinical Roentgenology of the Digestive Tract. By Maurice Feldman. Baltimore, William Wood, 1014 pp., 1938.

THIS is a monumental work which covers well every phase of the roentgenology of the digestive tract. It is well and interestingly written, and few words are wasted. Plenty of headings help the reader to find promptly the particular bit of information that is wanted. There are 358 illustrations which are well printed on good paper so that they show what the author intended them to show.

Extremely valuable to the student and to the writer are the extensive bibliographies at the end of each chapter which give an entrée to the literature.

The man who wants to know how common certain diseases are or what are the probabilities that a puzzling lesion is this or that will find many fine statistical tables to help him. The author is to be congratulated on the wisdom with which he refused to force his enormous material into the old moulds of the chapter headings of the old books.

To judge of the author's wisdom we looked, of course, to see if he agreed with us on certain controversial subjects, and were delighted to find that he does! For instance, in a carefully worded chapter he admits his inability to diagnose chronic appendicitis from the appearance of the appendix in the roentgenogram. With the terrible pressure constantly being brought to bear on the consulting roentgenologist to diagnose chronic appendicitis frequently and positively,

the making of such a statement requires courage and integrity of a high order.

Obviously the making of this book must have been a labor of love. No one but an idealist could have forced himself through the several years of grueling work in all spare hours of the day that are required for the completion of such a big and carefully documented volume. All roentgenologists will want to have a copy within reach, and all of us who are interested in gastro-enterology have been placed in Doctor Feldman's debt.

Food and Physical Fitness. By E. W. H. Cruickshank. Published by Wm. Wood & Co., Baltimore, 148 pages, 1938.

THIS is a practical little volume on the subject of foods, vitamins, mineral salts, nutrition, etc. It is small enough so that a busy practitioner can get quickly the available information and for that purpose quite adequate. There is so much information in this little volume, packed in so to speak and condensed that it should be on the bookshelf of every physician. For the busy man it is impossible to read everything coming out in this rapidly growing field and this book is meant to give such information with the minimum amount of time involved and for that reason should be read, studied and kept as a reference. The price of it being low, two dollars, makes it easily accessible to everyone.

Henry J. John, Cleveland.

Abstracts

RAILWAY SURGEONS TO MEET IN CHICAGO

Never before in the history of the Railway Surgeons have problems been so grave economically, or technique and treatment procedures of such import as they exist this year. The 23rd annual meeting of the American Association of Railway Surgeons will be held at the Palmer House, Chicago, September 19th to 23rd, 1938. This association includes members in practically every railroad company in the United States, as well as the separate group organizations, embracing railroad surgeons of the New York Central System; Southern Railway; Atlantic & West Point R. R.; Western Ry. of Alabama; Illinois Central System; Chicago, Milwaukee, St. Paul & Pacific R. R.; Rock Island Lines; Chicago, Burlington & Quincy R. R.; Chicago and Northwestern R. R.; the Georgia Railway and other road associations. An extremely interesting and highly profitable program has been arranged and all physicians and surgeons are invited to attend the sessions of this meeting as guests of the organization. There will be no registration fee to M.D. non-member guests. In addition to the scientific exhibits, a technical show will be held, including the presentation of new equipment, advanced types of therapy, new pharmaceutical and biological products and the latest techniques in many branches of the profession. A cordial invitation for you to attend is extended by Dr. Harvey Bartle, President of the Association. Complete program and information regarding the meeting and the exhibits may be secured by addressing Mr. A. G. Park, Convention Manager, the American Association of Railway Surgeons, Palmer House, Chicago, Illinois.

CONNOR, CHARLES L.

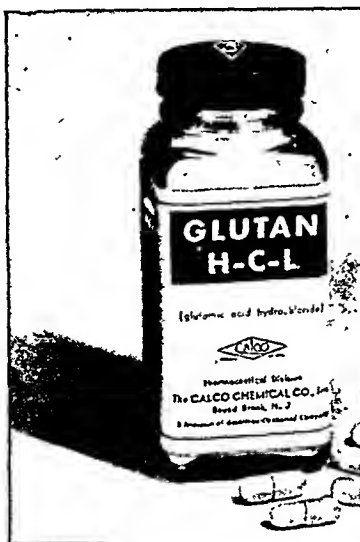
Fatty Infiltration of the Liver and the Development of Cirrhosis in Diabetes and Chronic Alcoholism. Am. J. Pathol., XIV, 3:82, 347, May, 1938.

"Direct evidence that alcohol can cause cirrhosis of the liver has been demanded before it is accepted as the primary etiological agent in so-called alcoholic cirrhosis, though everyone knows that the association of the two for centuries has been that of a cause and effect relationship." With this opening statement the author introduces the underlying theme of his study.

The mechanism by which cirrhosis of the liver develops has not been understood. The author reviews

briefly the history of the subject from the observations of Rokitsky (1849), on the presence of fatty livers in heavy drinkers of spirits to the present day knowledge of the association of fatty infiltration and cirrhosis of the liver in diabetes and chronic alcoholism and the experimental production of true portal cirrhosis in depancreatized dogs (Chaikoff, Connor and Biskind. *Am. J. Path.*, XIV, 1:80-101, Jan., 1938).

From his own study of autopsy material and clinical and experimental data and that of other workers the author comes to the following conclusions. Long continued fatty infiltration of the liver is a mechanical factor of great importance in the development of a fibrous tissue retaining wall around distended lobules. Collapse of liver sinusoids and pressure on the peripheral cells of the lobules leads to



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a reduction in circulation and a consequent anoxemia. Slow atrophy of the cells is the usual result. The liver that develops extensive cirrhosis has withstood the more acute degenerative changes over a comparatively long period of time.

Connective tissue proliferation begins anywhere in the periphery of the lobules from the cells forming the walls of sinusoids. Frequently it is more prominent around the portal areas but not necessarily so.

From the swollen cells of the sinusoids a delicate reticulum forms around the degenerating liver cells. Fibroblastic proliferation follows these lines and joins with prolongations from the periportal connective tissue. These strands of growing fibrils often define more or less clearly the limits of the lobules, but they also cut across them and form an irregular lobulated pattern.

The disappearance of fat from the liver in advanced cirrhosis may be

due to a combination of factors. The exhaustion of the fat reserves of the body due to gradual starvation is one. When the cirrhosis brings about a chronic passive congestion of the gastro-intestinal tract the amount of alcohol ingested is often reduced and a better diet resumed. Increased intake of carbohydrates, especially of glucose, causes fat to disappear rapidly from the liver. Frequently, as seen at autopsy, all signs of fatty infiltration have disappeared and the quiescent, fibrotic, nodular liver of alcoholic cirrhosis is found.

Fatty infiltration of the liver occurs in those conditions where, because of lack of intake or absorption of food, fat is mobilized from the existing fat depots; and where, because of disturbed metabolism of fat due to anoxemia or tissue anoxia, the accumulated fat in the liver cannot be broken down for use. In the first place it results from external starvation; in the second from an internal or tissue starvation. In both instances normal carbohydrate-fat metabolism does not take place. These states occur frequently in wasting diseases, as diabetes, or in chronic intoxications which inhibit proper tissue oxidation, as in chronic alcoholism. In the latter state actual starvation and a vitamin B deficiency are also usually present. It must be believed that a liver which contains demonstrable neutral fat is in most cases pathological. Its presence may be great enough to disturb seriously both the metabolic and the mechanical functions of the organ. The development of perilobular fibrosis seems to be the result of a combination of mechanical pressure, local tissue anoxia and general anoxemia, which cause atrophy and degeneration of the liver cells.

The alcoholic liver occurs in two forms, one of which is the precursor of the other. The first is the large tense liver, swollen with fat. The excretion of bile and the transmission of portal blood may be so interfered with by increased intrahepatic pressure that clinical jaundice and ascites are present. Such patients frequently die in coma and show at autopsy a large fat liver as the only prominent finding. The lobules are distended with fat and the peripheral cells show hyaline degeneration and atrophy with an early proliferation of fibroblasts. In the second form the proliferation of connective tissue has advanced to the point of showing the typical picture of portal cirrhosis as seen in chronic alcoholism. The gradation of the one into the other is so manifest that the author believes the true mechanism of the production of alcoholic cirrhosis seems to have been definitely demonstrated. The absence of fat in such livers at the end is explained by the exhaus-

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1. "The Vitamin B Complex and Functional Chronic Gastro-Intestinal Malfunction: A Study of Two Hundred and Twenty-Seven Cases" by Drs. Borsook, Dougherty, Gould and Kremers, in Am. Jr. of Dig. Dis., June, 1938. Reprint available on request.
2. Relation of Vitamins to Enzymes. J. A. M. A., July 2, 1938, Page 28.



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N. W. Jones, Portland.

STREET, A.

"Disease of Gall Bladder and Bile Ducts—Symptomatology and Results of Surgical Treatment." *Southern Surgeon*, 7:299-305, Aug., 1938.

Poor results following biliary surgery for chronic complaints is often attributed to preoperative disease with damage to the liver, pancreas and bile ducts. Incomplete surgery and recurrence of the original disease are also factors. However, a definite number of failures are attributable to the fact that the preoperative symptoms were either caused by disease unrelated to the biliary tract or by non-surgical liver disease. The present study of 197 operated cases was an attempt to appraise the value of symptomatology as an aid to correct diagnosis and prognosis.

Chronic gall bladder disease must be differentiated from (1) nutritional deficiency disease, characterized by malnutrition, weight loss, sore mouth, burning esophagus, smooth tongue, low free hydrochloric acid, and anemia; (2) psychoneurosis with its aerophagia, belching, indigestion, mucous colitis, and insomnia, and (3) less commonly, migraine, arthritis of spine, digestive disturbance of pulmonary tuberculosis, and syphilis of the central nervous system.

Acute gall bladder disease may be confused with acute appendicitis, acute pelvic peritonitis, pneumonia with abdominal pain, coronary thrombosis, gastric crisis of tabes, lead colic, etc.

Significant findings in this review are the preponderance of females, the increased prevalence in the fourth, fifth, and sixth decades, the high incidence of previous typhoid infection, definite weight loss (greater in common duct obstruction) and abdominal pain or colic. This latter appears to be the most dependable of subjective symptoms. The attacks of pain are usually irregular with comfort between seizures. The pain is most often in the epigastrium and appears at greatly varying times after eating. Radiation to the back is more common in common duct disease.

Of the postoperative cases of this series the group obtaining the highest percentage of complete relief were the common duct cases. It is suggested that better results will follow low gall bladder surgery if the symptoms are more carefully evaluated, emphasizing particularly the importance of pain rather than vague per-

sistent digestive symptoms. The fact that patients with more advanced disease may obtain better results, aside from surgical mortality, than those with apparently slight disorders can probably be explained by the greater accuracy of diagnosis and the more certainty of the type of therapy indicated in the severe cases.

J. Duffey Hancock, Louisville.

GRIMES, ALLEN E. AND MASSIE, FRANCIS M.

Regional Ileitis: (With Reproduction of a Case in 1806). Southern Surgeon, 7:251-262, June, 1938.

Regional ileitis represents an acute, subacute, or chronic necrotizing and cicatrizing inflammatory condition, not necessarily limited to the ileal segment of the bowel. It usually occurs in the third decade and affects males twice as often as females. The definite etiology is unknown but the disease in man is probably due to a chronic low grade bacterial infection.

The course of the illness may be acute and fulminating or chronic of several months duration when first observed. The fulminating type resembles other acute intra-abdominal inflammatory conditions, especially



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appendicitis, from which it may be impossible to make a differential diagnosis. This acute phase may be followed by diarrhea and other symptoms suggesting chronic ulcerative colitis. If healing does not occur chronicity leads to fibrosis deformity and obstruction at which time the clinical symptoms will be diffuse abdominal cramps, nausea, vomiting, distention, and borborygmus. A mass can generally be palpated because of the tendency for the bowel to become adherent to the anterior abdominal wall and adjacent vis-

cera, more frequently the right colon, but also the sigmoid. This adherence to surrounding structures probably accounts for the fistulae which sometime occur. X-ray examination may be of great aid in the chronic cases if the characteristic "string sign" is present. This is evidenced by a thin slightly irregular linear shadow suggesting a cotton string in appearance and extending from the area of the defect to the ileocecal valve—this shadow remaining constant for hours or even days.

Since spontaneous resolution has

occurred without operation or following simple exploration, medical management for all cases has been advocated by some. However, most advocate one of the following surgical procedures, ileocolostomy alone, ileocolostomy with subsequent resection, or one-stage ileocolostomy combined with resection. Ileocolostomy in poor risks with secondary resection if required is probably the best plan of procedure. Recurrence may follow even a radical resection. The general mortality of the disease has been estimated at 14%.

In addition to complete reports of three personal cases there is included an interesting account of "A Singular Case of Stricture and Thickening of the Ileum" reported before the Royal College of Physicians in London, July 4, 1806, by Drs. Charles Combe and William Saunders.

J. Duffey Hancock, Louisville.

STONE, CHARLES T. AND SHECKLES, LOYD W.

"Intestinal Tuberculosis: A Pathological and Clinical Survey." *Southern Med. Jour.*, 31:715-720, July, 1938.

Although tuberculosis of the intestine is the most frequent and one of the most serious complications of pulmonary tuberculosis it has not received the attention its importance should demand. This apathy is probably due to the difficulty of diagnosis, the feeling that it is a rather terminal lesion and the belief that it is not amenable to treatment. In a review of 2,220 consecutive autopsies, 284 or 12.9% were found to have tuberculosis in some form, 273, or 12.3%, had pulmonary tuberculosis and 60, or 21% of the total (284) had intestinal tuberculosis, or 22% of the pulmonary cases.

A study of these sixty cases serves as the basis for the observations that follow. The disease was most common in the third to sixth decades inclusive, it was more than twice as frequent in negroes and males predominated. Fifty-eight of the sixty cases showed pulmonary tuberculosis and cavitation was present in fifty-two of these fifty-eight cases. None of the cases showed the disease primary in the digestive tract. The site of preference of the intestinal lesion was the ileocecal region with a greater preponderance for the ileal side. The histories of the patients showed that the chief complaints as stated by the patients were referred to the digestive tract in eighteen cases (twelve of these having pulmonary symptoms as well). In thirty of the cases the chief complaint was entirely referable to the pulmonary system. The duration of the intestinal symptoms, except in three or four cases, was quite short. The most common gastro-intestinal symptoms were an-



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orexia (often present in uncomplicated pulmonary tuberculosis), abdominal pain, vomiting, and diarrhea. Abdominal tenderness and gaseous distention were the most common physical signs. Gastro-intestinal X-ray study was made in only two of the cases and in neither was the diagnosis made by this means. A clinical diagnosis of intestinal tuberculosis was suggested in only eleven of the sixty proved cases.

Since ultraviolet irradiation alone or combined with X-ray therapy and used concurrently with the general

treatment of tuberculosis ameliorates distressing symptoms and in a fair number of cases is productive of healing additional methods of study must be developed for the earlier diagnosis of the disease. Probably gastro-intestinal X-ray examinations as thorough as those made of the chest may prove to be of great aid in recognizing this complication which which may so impair the digestion and augment the toxemia present as to precipitate a crisis in the patient with a primary pulmonary lesion.

J. Duffey Hancock, Louisville.

WHITE, RICHARD JOSEPH.

"The Persimmon Phytobezoar—A report of three cases." *Southern Med. Jour.*, 31:750-755, July, 1938.

Human bezoars include the trichobezoar or hair ball, which is by far the most common, the trichophytobezoar, which is primarily hair mixed with fibers of vegetable matter, shellac concretions usually found in painters or shellac workers, and the phytobezoar or food ball by far the most frequent of which is the one caused by persimmons. Bismuth subcarbonate, massive doses of salol, tobacco, etc., have been reported as causing bezoar formation.

Persimmon bezoars are compact putty-lime masses varying greatly in size being frequently multiple. They are fairly soft, can be broken up or molded rather easily and may pass out into the small intestine which may become obstructed. Those fairly fresh have a greenish yellow color. Although it is uncertain why the ingestion of persimmons, usually harmless, should result sometimes in the formation of a bezoar, it is significant that most patients give a history of being unusually hungry and eating ravenously and in great haste of persimmons alone.

The effect of the persimmon ball on the stomach is dilatation of the stomach with redness, congestion, edema and in some instances hemorrhage and ulceration. The acute symptoms are those of a severe gastro-enteritis with vomiting, cramps, purging and fever. These may be followed by a sense of weight in the abdomen, severe nausea, and occasional mild vomiting of water or mucoid substance. Ingestion of food may aggravate or relieve the pain. All the symptoms may vary greatly in intensity. Movable filling defects are the outstanding observation on X-ray examination. Many mistakes in the differential diagnosis of these tumors have been made.

Brilliant results follow surgical removal by gastrostomy or enterostomy. The incision in the stomach should be large enough to admit the examining hand in order that multiple bezoars may not be overlooked. No treatment of the secondary ulcer is indicated as it will heal after the removal of the persimmon ball.

Three interesting cases are reported.

J. Duffey Hancock, Louisville.

STERN, J. E.

Abdominal Manifestations of the Hyperactive Carotid Sinus Reflex. *J. A. M. A.*, 110:1986, June 11, 1938.

Abdominal manifestations of the hyperactive carotid sinus reflex are rare. In this discussion the author

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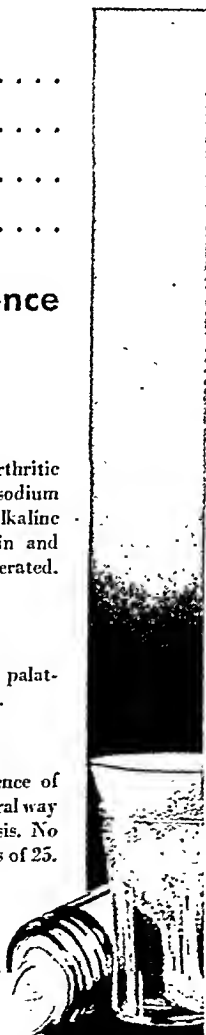
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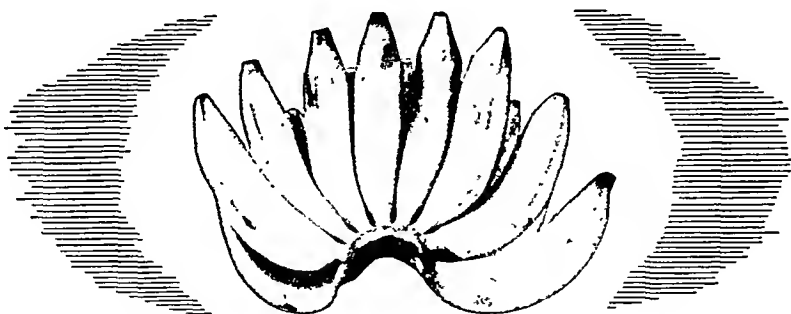
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states that the condition was characterized by abdominal cramps and diarrhea in conjunction with severe autonomic disturbance.

Weiss has divided these reflex responses into vagal, depressor and cerebral. The vagal and depressor types are associated with decreased cerebral flow and cerebral anoxemia. The vagal effect is characterized by cardiac slowing or asystole and can be modified with atropine depression of the vagus or with ephedrine and epinephrine stimulation of the ventricle. The depressor effect is char-

acterized by reflex vasodilatation by way of the aortic depressor nerves and is modified by ephedrine and epinephrine but not by atropine. The cerebral type is not associated with cerebral anoxemia and is probably due to a reaction in the vegetative centers of the hypothalamus.

Vagal-depressor and cerebral-depressor syndromes occur and are characterized by dizziness, weakness, hyperpnea, facial pallor, bradycardia, numbness and tingling of the extremities, convulsions, drowsiness, cataplexy, epigastric distress, nausea,

lacrimation, cough, amnesia and palpitation.

The author presents the case of a man who since 1928 had been having attacks of sudden tightness and fullness in the head, confusion, sweating of the hands followed by loss of consciousness. In September, 1936 he developed abdominal cramps, followed by an apparently normal bowel movement. On leaving the bathroom he noticed some cerebral symptoms similar to his other attacks. He again developed abdominal pain and returned to the bathroom where he fell unconscious. Physical examination and laboratory examination were negative. Stimulation of the carotid sinus resulted in symptoms similar to those described in his attacks. He was put upon pheobarbital and atropine and was given atropine, Gr. 1/150, for the acute attacks. In spite of this he had several severe attacks. The right carotid sinus was denervated surgically and subsequently the patient has been free from attacks.

Francis D. Murphy, Milwaukee.

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1. Council on Foods, Jour. Amer. Med. Assoc., 108, 1252 (1937).
2. Factors Influencing Vitamin C Content of Vegetables, Trezler, D.K., Amer. Jour. Public Health, 26, 505 (1936).
3. Vitamin C Content of Vegetables, Mack, Trezler & King, Food Research, 1, 231 (1936).
4. Vitamin C in Canned Strained Vegetables, Flora Hanning, Jour. Nutrition, 12, 405 (1936).

ROSENBERG, D. H., ARENS, R. A., MARCUS P. AND NECHELES, H.

Beuzedrine Sulfate: Its Limitations in the Treatment of the Spastic Colon and a Pharmacological Study of Its Effects on the Gastro-Intestinal Tract. J. A. M. A., 110:1394, June 11, 1938.

Benzedrine sulphate has of late been used for a great many conditions. Myerson and Ritno found it to be of value in relaxing the spasm of the gastro-intestinal tract and the pyloric sphincter. They found it useful in spastic colitis and pylorospasm. The authors studied its action in this condition and its pharmacologic action on the gastro-intestinal tract.

In a series of eighteen patients of whom all but two had been receiving and not responding to the usual orthodox treatment, benzedrine sulphate in doses of 5 to 10 mg. was used before breakfast and lunch and in three cases before supper. The results were as follows: three were improved, one was improved but recurrence followed, eleven were unimproved, and three became worse. The drug was found also too unreliable in the uniformity of its results as evidenced by roentgenographic examinations in five patients.

Further investigation showed that on two normal subjects and in the dog it produced pylorospasm, enterospasm and prolonged the emptying time of the stomach.

The authors believe that this drug should not be used in spastic disorders of the gastro-intestinal tract.

Francis D. Murphy, Milwaukee.

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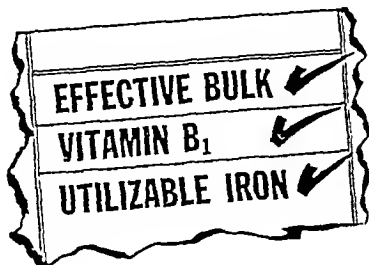


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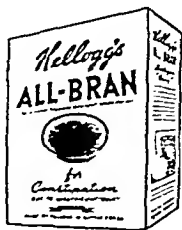


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These contributions by Kellogg's All-Bran to important physiological functions suggest its use as a dietary aid in constipation resulting from lack of bulk. Made by Kellogg in Battle Creek.



BATE, ALEXANDER.

Cancer. Kentucky Med. Jour., July, 1938.

The author attempts to build up an explanation of the etiology of cancer on the basis of a disturbed hydrogen ion concentration of the cells; this disturbance is attributed to faulty endocrine supply. The hypothetical mechanism involves distortion of the assumed intracellular electrical phenomenon within the mutated cell. The thymus gland is held up as the particular endocrine involved. The paper includes considerable recondite argument and involves references to physiology, physics, histology and even psychology.

The contribution presents difficult reading because one is not usually given so broad a field of speculation, and it may be said that it falls into a group of writings which while they perhaps carry little conviction to the reader, are not necessarily without a certain stimulating value.

CONNOTATIONS

By H. J. SIMS, M.D.

Denver, Colorado

In 1886, Lin successfully resected a portion of the liver. Brunn, in 1870, removed a small hepatic tumor.

Endothelioma of the ovary was recognized by Leopold in 1874. He used the term "lymphangioma cystomatosum." The term "endothelioma" was first used by Golgi, in 1869. Pick, in 1894, made a detailed study of this class of tumors and from a morphological standpoint divided them into three classes.

Hotz, of Chicago, successfully used the Thiersch graft for a symblepharon, in 1893.

Leyden, in 1884, suggested that typhoid perforation might be sutured. Mikulicz, in the same year, carried out such a procedure.

It is generally accepted that J. L. Petit, in 1772, was the first clinician to mention subcutaneous rupture of the tendons. Sédillot, in 1786, prepared an essay on this subject. It is believed by some historians that Hippocrates referred to muscle rupture. It is not clear whether Hippocrates referred to subcutaneous rupture or wound rupture.

Gould and Pyle report the case of Gerauld, in which a German woman, 84 years of age, maintained a vaginal pessary more than 50 years.

His, in 1866, first used the term "endothelium" and employed it to describe the cells lining all body cavities not admitting air. Ranvier extended its use to include cells lining lung alveoli.

Morton, of Philadelphia, and Sir Frederic Treves claimed to be the first to remove the appendix, in 1877. It is believed by many that priority should go to Kronlein of Germany, who, in 1884, removed the appendix on the advice of Mikulicz.

Fitz, of Boston, as early as 1886, advocated early removal of the appendix. Symonds of England, and Hall, of New York, successfully diagnosed and removed the appendix in the same year.

Hamilton, in 1884, collected 24 cases of axillary vessels torn in reducing old shoulder dislocation. Fifteen of them died.

Echinococcus of the heart was first recognized by Price, in 1821. Grulee, of Chicago, was the first in America to report echinococcus disease of the heart.

Karl Schroeder of Berlin, in 1880, was probably the first to open the abdomen for rupture of the uterus with a child in the abdominal cavity.

Rokitansky, in 1842, recognized status lymphaticus but confused it with tuberculosis of the lymphatics.

Spine Bifida was recognized by Sherwood, in 1813.

Cavernous angiomas in voluntary muscles, while not common, was recognized by Campbell de Morgan, in 1864. The tumor was congenital and occurred in a girl 10 years of age.

Radical operation for the relief of malignancy of the

RECENT ADVANCES IN THE SCIENCE OF NUTRITION

I. THE ROLE OF RIBOFLAVIN IN HUMAN NUTRITION

● In 1933, a series of articles on the vitamins was published, each article written by an authority in the field of nutrition. These papers served to summarize existing knowledge concerning these essential factors. During 1938 a similar series of articles has been issued. Comparison of related papers in these two series will indicate the most important advances in the science of nutrition which have been made in the course of the past five or six years.

In the first series of articles mentioned above, only two of the better known members of the old vitamin B complex received extended discussion (1). The more recent series, however, is characterized by the inclusion of a number of papers on riboflavin which, since 1932, has assumed a new significance in human nutrition (2). As compared with other factors with which it is often associated in nature, the rise of riboflavin to importance in human nutrition is somewhat anomalous.

For example, the effects upon humans of severe dietary deprivation of vitamin B₁ and the P-P factor are well known, in fact, such effects in themselves afford proof of the indispensable nature of these factors. While riboflavin is apparently concerned in cellular oxidation processes of mammals, the specific effect on humans of riboflavin deficiency is not known. Nevertheless, from the weight of evidence accumulated during the last five years, riboflavin is generally accepted as important in human nutrition. Authoritative opinion concerning riboflavin has been succinctly expressed as follows:

"The fact that we do not know any specific human disease due to shortage of riboflavin is entirely compatible with the view that this substance is important in human nutrition. A detailed discussion of reasons for believing that riboflavin plays a role in the life process of the human as

of other species would probably seem superfluous to a majority of readers at this date, and to a still larger majority in the future. Suffice it to point out that our species has evolved in the direction not of shortening the list of things it needs but of lengthening the list of things it can use to advantage." (2c)

Chemically, riboflavin is described as 6, 7 dimethyl-9 (d-l' ribityl) iso-alloxazine; a yellow-green, heat-stable pigment enjoying wide distribution in the plant and animal kingdoms. Many foods, therefore, of both plant and animal origin supply valuable amounts of this essential factor, specifically, fruits, vegetables, particularly the leafy pigmented types, and animal products such as milk and dairy products, meats, liver, and fish. It may, perhaps, be too early to estimate the daily human requirement for riboflavin. However, one rather liberal recommendation lists 600 units* as required daily by older children and adults; the estimated riboflavin requirement for younger children is somewhat less (2e).

In view of the above facts, attainment of an adequate intake of riboflavin would appear to be best insured by a varied dietary regime which includes the so-called "protective" foods. In the formulation of such diets, commercially canned foods may be particularly valuable. The older "vitamin C" assays—which are now known to measure principally the riboflavin contents of foods—indicate that modern canning procedures are without significant effect upon riboflavin. In addition, many foods valued for their contribution of this factor are canned commercially and hence are conveniently available at all seasons on practically every American market. Therefore commercially canned foods may be freely used in arranging such protective diets and they should materially assist in providing an adequate supply of this newly recognized dietary essential, riboflavin.

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*Bourquin-Sherman
1 1932 J. Amer. Med. Assn. 98, 2201 and 2283
1932. Ibid. 99, 26 and 121.

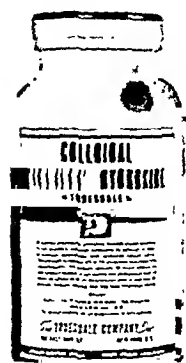
2a. 1938 J. Amer. Med. Assn. 110, 1105.
b 1938 Ibid. 110, 1188
c. 1938 Ibid. 110, 1278.

This is the fortieth in a series of monthly articles, which summarize, for your convenience, the conclusions about canned foods reached by authorities in nutritional research. We want to make this series valuable to you, so we ask your help. Will you tell us on a post card addressed to the American Can Company, New York, N. Y., what phases of canned foods knowledge are of greatest interest to you? Your suggestions will determine the subject matter of future articles.



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stomach was first performed by Pean, in 1879, and by Rydygier, in 1890. Billroth, in 1881, reported a successful operation.

Ponfick, in 1889, found that forty per cent of the liver could be removed without fatal results. In a series of animals, seven-eighths of the liver was resected and forty per cent of the animals survived. He determined if three-fourths of the liver was removed that regeneration replaced four-fifths of its normal weight. Gluck, in 1890, verified these findings.

In 1803, Portal attempted to classify mesenteric cysts. Augagneur, in 1886, was able to collect 96 cases of mesenteric tumors, 18 of which were cystic. Hahn, in 1877, classified mesenteric cysts on the basis of their contents, namely: blood, chylous, serous and echinococcus cysts.

Desprès, in 1880, reported a carcinoma of the rectum in a child six years of age. This case report has been mentioned in many articles and in text-books. The original article states the child was sixteen years of age. No microscopic examination of the tissue was made.

Küster, in 1896, made use of a transverse suprapubic incision for cosmetic effect. Rapin of Geneva, about the same time, unknowingly introduced the same incision for the same reason. Pfannenstiel, in 1900, modified the transverse incision, believing that less chance of hernia was possible. Stimson, in 1902, unaware of Pfannenstiel's publication described the same incision.

McKNIGHT, R. B.

Appendicitis: A Problem for Public Health Agencies as Well as for Practising Physicians. Southern Med. and Surg., 100:281-283, June, 1933.

Laxatives and delay account for nine out of ten deaths from appendicitis. A survey in Philadelphia covering some 15,000 cases showed that of the patients admitted to the hospital within 24 hours of the onset of the attack, 1 in 49 died, within 48 hours 1 in 21 died, within 72 hours 1 in 16, and after 72 hours 1 in 11 died. As regards laxatives, where no laxative was given 1 in 71 died, where one laxative was given 1 in 18, and where more than one was given 1 in 8 died.

It is a generally accepted fact that purgation and procrastination account for 90 per cent, or over, of the deaths from appendicitis. It is estimated that in the United States, appendicitis causes an annual loss of over \$100,000,000, approximately 90 per cent of which could be, and should be, saved.

The author urges closer cooperation between medical societies and boards of health in an effort to better acquaint the general public with the dangers of self-medication or delay in seeking proper medical advice in cases of abdominal pain or distress. Reference is made to the good results achieved in Philadelphia as the result of an educational campaign.

Hanes M. Fowler, Fort Wayne.

METZ, M. HILL AND LACKEY, ROBERT W.

Peptic Ulcer Treated by Posterior Pituitary Extract. Texas State Jour. of Med., 34:214-220, July, 1938.

The authors report satisfactory clinical results in 40 of 42 patients with peptic ulcer treated with posterior pituitary preparations. The duration of treatment averaged twenty-eight days, but subjective improvement was present after one to eight days. The use of posterior pituitary preparation in treatment was suggested by the observation of polyuria associated with the ulcer syndrome.

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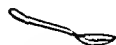
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RUSK, H. A. AND NEBER, E. N.

*Rupture of the Gall Bladder
Without Associated Cholecystitis.*
J. A. M. A., 110:1826, May 28,
1938.

Spontaneous rupture of the gall bladder complicating cholecystitis and cholelithiasis is rare. Rupture without inflammation or stones has not been reported.

The authors present the case of a man whose first complaint was the failing of vision and nocturia. Physical examination revealed a definite severe hypertension with retinal arteriosclerosis, and the electrocardiogram showed coronary disease. Laboratory examination revealed the presence of albumin, red and white cells and granular casts in the urine, but otherwise there were no abnormalities. He was put upon the usual hypertensive cardiac routine and responded for a short time. This was followed by a period of severe cardiac decompensation which was first treated in the hospital and later at home. One morning after being at home he was seized with an excruciating pain in the right upper quadrant associated with a coffee ground vomitus. He was readmitted to the hospital in shock. The blood pressure at this time was 268/100, the temperature 97.2° F. and the respirations 24. A very tender mass was palpable in the right upper quadrant, but there was no rigidity. The blood count was as follows: white cells 6,200, of which 8 per cent were stab cells, 74 per cent segmented cells, 18 per cent lymphocytes, and 1 per cent monocytes; red cells 3,560,000; hemoglobin 67 per cent. A tentative diagnosis of mesenteric thrombosis was made and he was given morphine and supportive treatment. He died 48 hours after admission.

Post mortem examination revealed the usual findings due to arteriosclerosis but in addition there was rupture of the gall bladder with fatal hemorrhage.

Frances D. Murphy

ABBOTT, W. O. AND JOHNSTON, C. G.

Intubation Studies of the Human Small Intestine. S. G. O., Vol. 66, No. 4, pp. 691-697, April, 1938.

The authors propose a method of small intestine intubation by means of which the entire small intestine may be emptied of its contents and the force of peristalsis at any point measured.

A No. 14 or No. 16 F. duodenal tube with a No. 3 F. rubber tube tied tightly to it is passed into the stomach of the patient. On the end of the larger tube is fastened a duodenal bucket while on the end of the smaller one is fastened a rubber balloon of 50 cc. capacity. As the ends of the tubes pass into the duodenum the balloon is

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inflated and suction is applied to the end of the larger tube. All intestinal contents are immediately removed and as normal peristalsis returns the inflated balloon is passed down the intestinal tract; the duodenal bucket preceding it. The tube will advance at the rate of about one foot per hour. Care should be taken to avoid its curling up in the stomach as that may inhibit its passage along the intestine. A length of between 8 and 10 feet will extend from the patient's teeth to the cecum.

As the balloon advances it will be stopped by an obstruction in the small bowel, which may be demonstrated roentgenologically by the injection of a small amount of dilute barium mixture. The nature of materials aspirated from the intestine may be studied and by attaching a manometer to the smaller tube the force of peristalsis may be measured.

The author feels that such decompression alone will render operation unnecessary in many instances and facilitate it greatly in many other instances.

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Four figures, a summary table, and some case reports accompany the article.

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GRAHAM, R. R.

Technical Surgical Procedures for Gastric and Duodenal Ulcer. S. G. O., Vol. 66, No. 2A, pp. 269-287, Feb. 15, 1938.

Surgical procedures have no place in the treatment of simple duodenal ulcer nor in the treatment of gastric ulcer before adequate non-operative therapy has been tried. The complications of duodenal ulcer such as perforation, penetration, hemorrhage and stenosis require surgical treatment. Surgical treatment of benign gastric ulcer will rarely be necessary if a carefully supervised and adequate period of treatment by intubation will be carried out. Such treatment should be continued over a 3 week period, after which the status of the ulcer is determined and further treatment decided upon. If under such treatment the ulcer is healed in 6 weeks, operation is not required. If after another 3 week period the ulcer has recurred, operation is indicated.

If operation is required for gastric ulcer a subtotal gastrectomy is the operation of choice. The author believes that any operation short of gastric resection and excision of the ulcer is inadequate for gastric ulcer. Either a posterior or an anterior type of Polya anastomosis, with a long loop of jejunum without entero-enterostomy is advised. A transfusion of 500 cubic centimeters of citrated blood is given during the operation.

In operations for duodenal ulcer the author prefers to excise the ulcer if it is reasonably possible and if it is a bleeding ulcer its blood supply should be securely ligated. A Finney type of pyloroplasty is quite satisfactory in certain types of ulceration with obstruction. In an elderly patient with low free hydrochloric acid and no history of bleeding, a pyloroplasty is satisfactory. In all others a gastric resection with removal of the pyloric antrum is employed by the author.

A large amount of technical detail is described. Sixteen figures, six tables and a bibliography accompany the article.

Nelson M. Percy, Chicago.

DIXON, C. F., DEUTERMAN, J. L. AND WEVER, H. M.

Diverticula of the Intestine. S. G. O., Vol. 66, No. 2A, pp. 314-327, Feb. 15, 1938.

The consensus of opinion is that diverticula of the intestine develop as herniations of the mucosa at points of entry of the veins. Supposed degeneration of venous connective tissue at those points leads to a weakness which gives way under increased pressure when other portions of the intestine contract. Meckel's diverticulum is a congenital abnormality.

Diverticula occur most commonly in the sigmoid colon and least commonly

in the ileum; about 18 per cent are found in the duodenum.

These structures when symptomless are looked upon as anatomical curiosities. In about one-fifth of the people with diverticulosis some inflammation supervenes and diverticulitis is present. Diverticulitis may lead to partial or complete obstruction of the bowel, or to perforation with abscess formation or perforation into another hollow viscus, forming an internal fistula. Meckel's, especially in children, is occasionally caused by bleeding from an ulceration in a Meckel's diverticulum.

The medical treatment of diverticulitis consists of bed rest, non-residue diet, liberal doses of belladonna and warm saline irrigations per rectum. Occasionally it is necessary to put that segment of bowel at rest by making a colostomy above the diseased part. The authors state that it was Judd's opinion that such a colostomy should not be closed before a year had elapsed.

Nine figures and a bibliography accompany the article.

Nelson M. Percy, Chicago.

MEANS, J. H.

Treatment of Peptic Ulcer—Indications for Surgery. S. G. O., Vol. 66, No. 2A, pp. 264-268, Feb. 15, 1938.

The author states that the etiology of peptic ulcer is unknown. It is important to differentiate simple ulceration from carcinoma and to determine whether the two conditions co-exist.

Surgery is indicated when medical treatment has failed and when certain complications are present, and sometimes when previous surgical treatment has failed.

Perforation is an urgent indication for immediate surgery. Just how much should be done is a mooted question. The author is of the opinion that a single hemorrhage in a person under 45 years of age is definitely not an indication for surgery, but repeated hemorrhage may be. A hemorrhage in a person over 45 years of age may be an indication for surgery, but there is a fair chance that he may never have another hemorrhage.

Pyloric obstruction when permanent and not due to spasm or edema is an indication for surgery. Resistance to medical treatment is a weighty indication for surgery. One should make certain that the treatment has been good and under proper conditions. The more a patient's problems harass him, the more their ulcers will plague them. Any patient with peptic ulcer should be under some treatment for the remainder of his or her life.

A large bibliography accompanies the article.

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CLARK, E. BROWN AND SHIELDS, WARREN.

Visceral Metastasis from Rectal Carcinoma. S. G. O., Vol. 66, No. 5, pp. 611-621, March, 1933.

The authors studied autopsy protocols of 170 patients who had carcinomas of the rectum within 15 centimeters of the anus, or who had had carcinomas removed from that region. Microscopic sections were studied in order to confirm the diagnosis and to look for tumor growth in blood and lymphatic vessels. This was difficult and in case of doubt the decision was made against intravascular invasion.

The tendency for rectal carcinoma to metastasize via the blood stream varies with the degree of differentiation. The type described by the authors as carcinoma simplex showed visceral metastasis in 56 per cent of the cases. Mucinous carcinoma has a tendency to metastasize via the lymphatics. As would be expected, the longer the duration of the carcinoma, the greater the number of visceral metastases. In only 5 per cent of the cases were metastases to bone found. Forty-one per cent of the cases showed visceral metastases; the liver being the most common site. The correlation between intravascular growth of the tumor and visceral metastases is closest in the

cases of longer duration. Visceral metastases were found in 21 per cent of the cases showing no lymph node metastases. A better prognosis may be rendered by determining the pressure or absence of intravascular growths than by determining the presence or absence of lymph node metastases.

Ten tables and a bibliography accompany the article.

Nelson M. Percy, Chicago.

LEWISOHN, R.

Segmental Enteritis. S. G. O., Vol. 66, No. 2, pp. 215-222, Feb. 1, 1932.

Segmental enteritis is at present a disease of unknown etiology. For that reason classification is difficult and proper medical or surgical treatment is not generally agreed upon. The author doubts whether segmental enteritis is a clinical entity; he feels that it may turn out to be a milder form of ulcerative colitis.

Fistulous communications between parts of the intestinal tract and symptoms of partial intestinal obstruction are prominent features in the clinical course of this disease. The author points out that peri-anal and recto-vaginal fistulas are occasionally seen also.

The treatment of this disease is distinctly surgical. Resection in one or two stages or sidetracking operations have cured the disease. If a sidetracking operation is elected, the bowel should be divided above the diseased portion and closed, insuring complete rest of that part. The presence of a fistula makes primary resection mandatory.

Six figures, one table, and a bibliography accompanying the article.

Nelson M. Percy, Chicago.

LICHTMAN, S. S.

The Association of Sciatic Neuritis with Liver Disease. Annals of Int. Med., 11:1992-1995, May, 1938.

The author reports five cases in which symptoms of sciatic neuritis preceded the onset of clinical evidence of liver damage and jaundice. In three instances the jaundice and liver disease occurred in persons who had not ingested cinchophen in any form.

These observations suggest that endogenous toxic substances, responsible for the peripheral neuritis involving the sciatic nerve, may also be responsible for the liver injury.

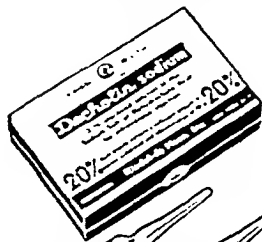
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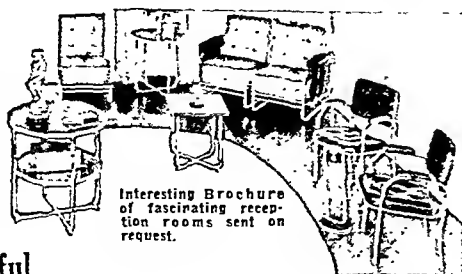
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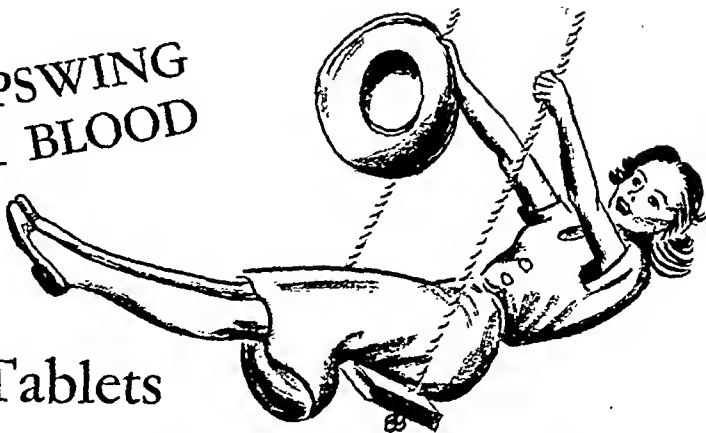


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Carbonate Excretion in the Urine as an Indication of Alkalosis

By

LEE C. GATEWOOD, M.D.
CHICAGO, ILLINOIS

A SEARCH of the literature reveals a dearth of data concerning the presence of carbonates in the urine, Denis and Minot (1) stating "In the course of our investigation of certain problems which involved the ingestion of small quantities of sodium bicarbonate it was found convenient to use the carbon dioxide content of the urine as a measure of bicarbonate excretion. In this connection the question at once presented itself as to what variations must be looked for in the excretion of urinary carbon dioxide under ordinary normal conditions. A consultation of the literature proved unfruitful. The recorded determinations of carbon dioxide are few in number and have been made under conditions of such diversity that correlation of the various results appeared difficult, if not impossible." They made a study of carbonate excretion and as a result of their studies they reached the conclusion that the amount of carbon dioxide in the urine of subjects taking ordinary mixed diets varied from 20 to 211 cc. per 24 hours and that the amount excreted varied with the reaction of the urine. Mitchell (2) discussed the available tests for alkaline carbonates in the urine, suggesting the use of mercurous nitrate for the determination of ammonium carbonate in the urine. Later he suggested the use of nickel sulfate (3) for the demonstration of the presence of soluble carbonates in the urine.

Gamble (4) made a further study of the factors which determine the elimination of carbonic acid in urine and reached the conclusion that the bicarbonate content of urine varied inversely with the urinary pH and that the elimination of carbonic acid in the urine was determined by the CO_2 tension of the blood plasma.

A study of the disturbances of acid-base equilibrium occurring in patients on alkali therapy for peptic ulcer (5) and the urinary findings which they presented brought to our attention some unexpected variations in the amount of carbon dioxide liberated from the urine when acid was added to it in the course of the usual tests for albumen. It was observed that some alkaline specimens of urine showed very little evidence of carbonate whereas others showed considerable amounts. The use of nickel sulfate as a test for carbonates and its clinical application to the problem in hand was then begun on my service with the help of one of my former assistants, Dr. John S. Ashby, and we were thus enabled to confirm and enlarge our previous observations.

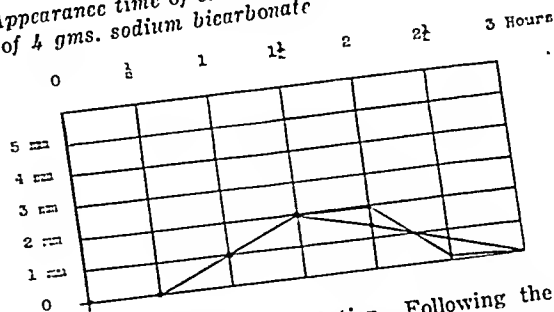
The technique of the test is very simple. Solutions of nickel sulfate in the presence of soluble carbonates precipitate a white cloud of nickel carbonate. For clinical purposes the test is most conveniently made in a conical glass into which is put a few cubic centimeters of 20% nickel sulfate solution. Filtered urine is then carefully overlaid by pouring the urine into a folded filter paper and allowing it to run gently down the side of the glass as in the familiar nitric acid test for albumen. The presence of soluble carbonate in the

urine is indicated by the formation of a white ring of precipitate at the point of contact of the two fluids. The thickness or density of the precipitate ring affords a simple means of making gross quantitative comparisons of the amounts of carbonate present in different samples of urine. The test has been found to be delicate enough to indicate the presence of small quantities of soluble carbonate in the urine, a 0.25% solution of carbonate in water yielding a positive reaction. It is suggested that those who have not previously used the test and may wish to do so, can readily familiarize themselves with it by testing specimens of urine to which known quantities of sodium bicarbonate solution has been added. The sensitiveness of the reaction varies somewhat with the reaction of the urine. In general the higher the acidity of the urine the less sensitive the reaction seems to be and its sensitiveness seems to be enhanced somewhat in alkaline urines. Specimens of urine to which a solution of sodium bicarbonate has been added have been allowed to stand for 24 to 48 hours and at the end of this time still show a typical precipitate with nickel sulfate solution.

The quantity of carbonate present in the urine of normal subjects upon a general diet is insufficient to produce a detectable ring. This has been determined by testing a considerable number of routine urine specimens with uniformly negative results.

However, the ingestion of sodium bicarbonate is followed within a short time by the appearance of carbonate in the urine in amounts sufficient to show a definite white ring of precipitate at the point of con-

TABLE I
Appearance time of carbonate in urine after ingestion of 4 gms. sodium bicarbonate



tact with nickel sulfate solution. Following the ingestion of 4 gms. of sodium bicarbonate the urine shows at the end of an hour sufficient carbonate to produce a positive reaction and this may continue to be present for as long as three hours after the ingestion of the soda though the maximum reaction is usually obtained at the end of two hours. Using phenolphthalein as an indicator there is a decrease in the acidity of the urine on titration with N/10 NaOH

TABLE II
Patients on ulcer management

Patient	Age	Date	Medication					Blood CO ₂	Nickel Sulfate Test		Remarks
			Calc. Carb.	Ca. Phos.	Mar. Phos.	Magn. Oxid.	Soda		Before Soda	After Soda	
Robert H. 267524	50	10-17-31 -19- -29-	5	15 10	15			63.6 57.0 57.6	0 + +	Tr. +++ +++	Hemorrhage
Miriam B. 256373	65	1- 5-31 - 9- -13-		10 10	10 10	10 10	10 10	61.7 72.8 60.7	0 0 0	+ 0 ++	Obstruction and continued secretion
Maurice B. 317962	20	6-16-36 -23- -26-	10	10 10	10	10 10	10	70.6	0 0 1 mm.	Tr. Tr. 10 mm.	
Ruth F. 313105	30	12-15-35 1-13-36	10	10	10	10 10	10 10	62.9	3 mm. 0	4 mm. 5 mm.	
Douglas W. 277885	72	10- 7-32	15			10	10	64.5	0	3 mm.	
Harriet A. 302362	70	2-27-35		15	15	5		54.8	++	++++	Obstruction
James H. C. 310313	45	10-30-35	20	15		10	10	66.4	0	3 mm.	
Maurice P. 304091	42	4-19-35	10	5		5		67.3	Tr.	1.5 mm.	
E. Rans. K. 340169	32	4- 1-38 - 3- -18-	10	10 10	10	10 10		65.5 53.2	0 0 0	0 0 +	Hemorrhage Alum. hydrox.
Charles P. 338440	54	2-24-38	10	10		5		68.9	0	0	
Thora A. 338503	46	2-24-38	5	5		5		64.3	0	0	
Ray S. 339286	52	3-15-38		10	10	5		57.0	0	+	Hemorrhage
Abramam W. 260293	71	1-10-33 -20-	10	10		10		57.9	0 0	++ (5 hrs.) +	Hypertension and diabetes
Solomon J. 258284	74	1-27-31	10			10	10	74.9	0	0	Hypertension and diabetes
Nora Z. 291381	40	2-17-34 3- 2-34	10	10 10		10		60	0 1	5 mm. 6 mm.	MgCO ₃
C. Well. K. 313514	65	2- 7-36	10	10		10		53.5	0	2 mm.	
Gus. G. DeC. 312562	55	12-28-35 1-11-36 -14-	10 10 10	10 10 10		10 10 10	10 10	74.8	5 mm. 8 mm. 0	11 mm. 14 mm. 0	
Ozro P. M. 298277	64	10- 1-34 - 4- -10- -15- -19-	10 10 10 10 10	10 10 10 10 10		10 10 10 10		70.2 61.7	0 0 0 0 0	11 mm. 11 mm. 9 mm. 0 6 mm.	
Jessie M. 259506	47	3- 4-31	10	10				64.5	0	0	
John M. 248511	39	4-22-30	20	10		10	10	70.2	0	++++	Continued secretion
George M. E. 291118	63	2-15-34	15	15		10		53.2	0	0	
Frederick S. 282296	49	2- 6-34 -14- -19-	15 10	15 10		10 10	10	56.2 71.1 65.5	Tr. 0 0	6 mm. 0 1 mm.	Moderate hypertension

corresponding to the increase in carbonate content. This is in conformity with the findings previously reported by Denis and Minot and by Gamble.

In earlier years when sodium bicarbonate was used rather generally in the alkali treatment of peptic ulcer it was found that the application of this test to the urine of such patients yielded quite regularly a positive carbonate reaction. However, upon the development of alkalosis there was as a rule prompt decrease in the excretion of carbonate to the point where this reaction could no longer be demonstrated. With return

to normal acid-base equilibrium there was a return of carbonate excretion. There is some variation in the level at which carbonate excretion disappears. In general it has been found to decrease below the level at which a positive nickel sulfate reaction can be demonstrated when the level of blood CO₂ combining power exceeds 65 volumes per cent and in only one instance has it been found to persist above a level of 70 volumes per cent. On the other hand there have been only rare instances in which carbonate excretion

was found to be materially diminished with blood CO_2 values below 60 volumes per cent.

At the time we began using this test a great many of the patients on alkali type ulcer treatment were receiving powders of which sodium bicarbonate was a component and it was, therefore, a simple procedure to test the urine of such patients with nickel sulfate. The finding of a heavy carbonate precipitate at the point of contact then provided a degree of assurance that the patient's acid-base equilibrium had not been seriously disturbed. If, however, the urine showed little or no evidence of carbonate content a blood CO_2 determination was immediately started and a change in therapy instituted.

For a number of years we have used little or no sodium bicarbonate in our program of ulcer therapy. The alkalies used, as indicated under the heading of "Medication" in the accompanying table, have been chiefly calcium carbonate, calcium phosphate, tri-basic magnesium phosphate and magnesium oxide. Occasionally we have used magnesium carbonate and more recently various preparations of aluminum hydroxide. In some instances the old combination of magnesium oxide and sodium bicarbonate has been administered for a few doses in the course of the day but the quantity of sodium bicarbonate taken in this way rarely exceeds thirty to sixty grains spread over the course of the day. It has been found that the administration of calcium carbonate in doses of 10 to 15 grains per hour as commonly used does not give rise to a positive carbonate reaction in the urine as tested with nickel sulfate. Some patients who have received larger doses of calcium carbonate have shown a positive carbonate reaction in the urine. In order to utilize this test clinically, therefore, it is usually necessary to provide a source of soluble carbonate and this may be done by giving the patient two or three doses of sodium bicarbonate instead of his usual alkali therapy. Practically, this has been done by giving the patient 30 or 40 grains of sodium bicarbonate at hourly intervals instead of the usual alkali dosage and obtaining a control specimen of urine before the first dose of soda and a specimen two hours later—one hour after the second dose of soda. Each specimen is tested with nickel sulfate solution. An individual with normal acid-base equilibrium will show, as a rule, no precipitate or only a trace in the control specimen and a definite carbonate ring in the second specimen.

In the accompanying table are shown records of a number of tests performed in this manner. The data therein presented are selected from the records of approximately one hundred cases in which this test has been used. Naturally most of these patients did not at any time present manifestations of alkalosis and the nickel sulfate reaction yielded a simple normal response. It has not seemed essential to multiply the presentation of such cases though a few typical examples are recorded in the table. Attention is called rather to those cases which present disturbance of acid-base equilibrium and to the corresponding urine test with nickel sulfate and particularly to those patients presenting normal carbonate secretion with blood CO_2 combining power within normal range and deficient carbonate excretion in periods marked by alkalosis.

It is manifestly undesirable to administer sodium bicarbonate for this test if the patient already presents findings such as to constitute a strong presump-

tion of alkalosis. There are found occasionally abnormalities of carbonate excretion which are not on the basis of alkalosis. For example some patients with nephritic nitrogen retention and consequent acidosis have shown deficient carbonate excretion. The test has been applied in several such cases and with some patients with cirrhosis and ascites who have been converted to a state of acidosis by the administration of ammonium chloride but the data available are thus far insufficient to warrant conclusions. The information available from this test is certainly not as accurate or conclusive as that from blood carbon dioxide determination and it is not proposed as a substitute therefor. It is, however, a very simple test to make, inexpensive and not time consuming. Since it has been found that there is relatively little change in the carbonate reaction of such urine specimens on standing and such specimens are readily transportable this test has occasionally proved valuable as an indication of acid-base equilibrium in patients who were located in places too remote for readily available blood CO_2 determination.

CONCLUSIONS

1. Nickel sulfate has been found a convenient reagent for the demonstration of soluble carbonate in the urine.

2. Patients who are taking sodium bicarbonate or other soluble carbonates excrete demonstrable amounts of carbonate in the urine as shown by this test.

3. In a state of alkalosis the carbonate excretion is markedly decreased or absent. With return to a normal acid-base equilibrium there is a return of normal carbonate excretion.

4. This test by reason of its simplicity and its applicability to transportable urine specimens presents a field of usefulness where, for various reasons, determinations of blood CO_2 combining value or pH are not available.

I wish to acknowledge the help of Dr. John S. Ashby and Dr. Mary Christine Gatewood.

DISCUSSION

DR. WALTER G. KARR (Philadelphia, Pa.): I believe Dr. Gatewood has emphasized a very important point in the acid-base balance of the body. We know that the kidneys have a large factor of safety. When acids are presented they manufacture ammonium salts. The phosphate buffer controls the acid base balance in the urine between pH 5 and 8. We have believed that the excretion of sodium bicarbonate directly by the kidney was a very efficient mechanism in regulating alkalosis. We have believed that mechanism was rather unlimited and with a good urine output the kidney could easily control almost any alkalosis; however, Dr. Gatewood has indicated quite definitely here that there seems to be a limit in many cases around 65 to 70 vol. per cent. plasma CO_2 , above which bicarbonate is not secreted in the urine.

This is rather a new idea and it explains to a large extent these cases of alkalosis which have appeared in the past, when bicarbonate therapy was more in general use. I believe about 5 per cent of those cases usually showed the signs of toxicity that you all know.

It is perhaps worth while to differentiate between this alkalosis which is definitely an alkali excess, and that alkalosis which occurs with a total electrolyte or total base loss from the body and originates with pernicious vomiting. We have in those cases a low total electrolyte in the body and it would be interesting to know if those cases respond in the same way as these cases with alkali excess.

It is obvious that in an acidosis, where the secretion of CO_2 is of necessity very low, this test will probably be negative. I believe that this work is an indication for a great deal more study of the acid-base mechanism in an experimental way. The mechanism of this alkalosis should be re-studied all the way through by animal experimentation.

Certain pathologists have talked about an alkalosis kidney, which I know absolutely nothing about, but undoubtedly that is related to the same condition.

DR. VICTOR C. MYERS (Cleveland, Ohio): I should like to ask a question of Dr. Gatewood. I do not recall that he explained why the carbonate excretion in the urine should be decreased or absent in alkalosis. It has been recognized for sometime that with a constant alveolar CO_2 tension there is a definite relation between the pH of the urine and its bicarbonate content, and that the bicarbonate content of the urine at a pH of 8 is ten times that of pH 7 and 100 times that at pH 6. In simple terms the bicarbonate increases with the alkalinity of the urine.

Even the CO_2 of the blood is not always an absolutely reliable indication of alkalosis. There may be some little

fluctuation in the CO_2 around the critical level without a change in the pH of the blood plasma. I have seen a high blood pH and clinical symptoms of alkalosis with a plasma CO_2 of 56 vol. per cent while on the other hand I have seen the plasma CO_2 rise to 70 vol. per cent before the pH of blood became abnormal. About eleven years ago Dr. Gatewood's brother and I reported a paper before this Association in which we called attention to a number of points dealing with chemical blood findings in relation to sodium bicarbonate administration and clinical symptoms of alkalosis.

It would seem to me that this test of Dr. Gatewood's should be of considerable usefulness if it obviates the need of much more complicated laboratory procedures.

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Variations in the Enzymatic Activity of Duodenal Contents*

Preliminary Report

By

VICTOR C. MYERS, Ph.D., D.Sc., ALFRED H. FREE, M.S.

and

ARGYL J. BEAMS, M.D.

CLEVELAND, OHIO

SINCE the introduction of the duodenal tube by Einhorn (1) in 1910 the estimation of the enzymatic activity or concentration of duodenal contents has received the attention of many gastro-enterologists and scientists in allied fields, and a considerable literature has accumulated on the subject. A marked reduction in enzyme activity has been observed in pancreatitis, while some reduction in the activity of the pancreatic enzymes has been noted in a variety of disorders, chiefly those which might have some influence on the pancreas. That no unanimity of opinion exists as to the most desirable methods to employ in measuring these enzyme activities is evidenced in the survey which was conducted by this Association (2) four years ago. Some of the methods employed have been hardly more than qualitative tests, while others, notably those of McClure and his co-workers (3) have yielded fairly reliable quantitative information on the concentration of the enzymes. The interest of one of us (M.) in this subject was revived due largely to a request to cooperate in the study of enzyme methods.

We fully appreciate the difficulty in making a significant contribution to a problem that has been studied repeatedly. We have felt, however, that with further refinement in methods, taking due account of the various factors involved in measuring the activity

of the duodenal enzymes, it should be possible to define normal values more accurately than has been done in the past.

The first purpose of the work we are reporting was, therefore, to establish a system of analysis which would give an accurate picture of enzyme activity. We believe that the methods which we have worked out do yield such data. It seemed essential that the methods should employ optimum conditions for the activity of the enzymes, including optimum pH, optimum buffer concentrations, optimum substrate concentrations, and should be based on the measurement of digestion products, rather than on the disappearance of the substrate. The principles underlying the methods we have used are not new, but we believe that adherence to certain exact details, and a new scheme of recording the results permit a more accurate definition of normal variations and thus an earlier recognition of pathological values.

It seemed necessary at the outset to ascertain for ourselves the optimum pH for the action of the protease, lipase and amylase of duodenal contents. If possible, we wished to employ the same buffer solution for all these enzymes. The buffer phosphate solution of pH 8.4 employed by McClure (3) and his co-workers seemed too high to us, considering the average pH of duodenal contents. As a matter of fact, we found relatively little difference in the proteolytic action on casein over a pH range of 6.8 to 8.4 and in the lipolytic action on tributyrin and triolein over a pH range of

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7.0 to 8.4. However, in the case of amylase the enzyme activity was definitely greater at a pH of 7.2, the sodium chloride concentration being held at the optimum of 0.05 M. This observation was of interest to us in connection with the fact that, although the pH of duodenal contents fluctuates over quite a wide range, from a pH of about 4.0 to more than 8.0, the average appears to be just on the alkaline side of pH 7.0. On this basis a buffer phosphate solution of pH 7.2 was employed in all our work on duodenal enzymes.

The principles of the methods developed for the estimation of the proteolytic, lipolytic and amylolytic enzymes in duodenal contents will be briefly outlined in an effort to visualize the technique we have employed. As indicated above the end products of digestion were used in each case as the measure of enzyme activity, viz., amino acid nitrogen for protease, fatty acids for lipase and reducing sugar (maltose) for amylase.

Protease Method. The method for protease (trypsin) was similar to that employed by McClure (3). We were unable to find a better protein for the substrate than casein. A number of different preparations of casein were tried and all found to be satisfactory. As noted above the pH was buffered at 7.2. After digestion for 30 minutes at 38° C. the residual casein was precipitated with trichloroacetic acid and the non-protein nitrogen determined in the filtrate. This was done colorimetrically with the aid of Nessler's solution after kjeldahl digestion of the filtrate.

In all experiments a measured portion of the filtrate was also treated with Folin's phenol reagent in a manner similar to that employed by Anson and Mirsky (4) in their method of estimating trypsin, using hemoglobin as the substrate. Almost identical results were obtained with the two methods. It would therefore make little difference which procedure was employed to obtain the final result.

Lipase Method. Two methods have been employed in the estimation of lipase, one in which tributyrin was used as the substrate and the other in which an emulsion of triolein was used. The latter is the method described by Crandall (5), with slight modifications. The procedure is the same with both methods after incubation. Neutralized ethyl alcohol is added and titration carried out with 0.1 N NaOH in 95 per cent ethyl alcohol using phenolphthalein as the indicator. Essentially the same results were obtained with both methods.

Objections have been raised to the use of tributyrin as a substrate for lipase determinations on the basis that it measures an esterase system rather than a lipase system. On the other hand it is generally conceded that true lipase attacks triolein (or olive oil). However, the preparation of a suitable olive oil emulsion offers certain technical difficulties. In our studies optimum buffer concentrations as well as pH and enzyme concentrations were established. The two methods gave comparable results in over two hundred specimens studied and no instances were noted where the interpretation of the results would be any different with one method than the other. Therefore if there are two distinct enzyme systems, a lipase and an esterase, they parallel each other and give similar results. Neither of the methods give a perfectly straight line relationship, such as is obtained with trypsin and amylopsin, but there appears to be a good relationship between the titration figures and the amount of enzyme present.

Amylase Method. The method employed for amylase (amylopsin) was a modification of the method introduced by Myers and Killian (6) to measure the diastatic activity of blood. As a matter of fact they also employed the method for duodenal contents. As already noted amylase is quite sensitive to pH when optimum concentrations of activating sodium chloride are used. The method was worked out to provide optimum pH (7.2) along with optimum NaCl concentration. A plicate method was used to estimate the maltose formed. As shown by Myers and Reid (7) this method is much more satisfactory than the Folin-Wu method for this purpose. Soluble starch was used as the substrate and several different preparations were found to be satisfactory. The method as employed gave an almost perfect straight line relationship, i.e., the amount of reducing sugar formed was directly proportional to the concentration of amylase over the range of enzyme concentrations found in human duodenal contents.

Duodenal contents were obtained in the usual manner with the aid of a Rehfuess tube, the position of the tube being checked in practically all cases with the fluoroscope. It soon became apparent that the fasting duodenal contents were quite irregular in enzyme activity. In all cases reported four samples of fluid were collected, all of which were analyzed, a total of considerably more than a 1000 determinations being made. A 20 minute fasting sample was obtained by siphonage following which 25 cc. of olive oil were injected through the tube into the duodenum. Ten minutes were allowed to elapse and then continuous siphonage established. The samples were divided into three fractions each representing the drainage over a 20 minute period. In addition to the enzymes, the icteric index was determined on all samples to obtain an idea of the amount of bile present, and the buffer value also determined on the fasting sample. The volume was also recorded so that the total enzyme output as well as the concentration could be calculated, if desired.

A group of 13 studies has been carried out according to the technique described on 9 normal individuals, including both sexes. In general the highest enzyme values were found in the 3rd or the 2nd specimen after stimulation with the olive oil, although this was not always true, and occasionally the highest value was found in the 1st or fasting specimen. At present it has seemed unwise to limit the analyses to one specimen, and the four specimens have all been analyzed. We are hoping ultimately to obtain a sufficiently potent pancreatic stimulant to make the analysis of more than one sample unnecessary.

For the present we are selecting as the criterion of potential enzyme activity the maximum value obtained in the four samples. This has been found, with but few exceptions, in the 3rd or 2nd sample. It is on the basis of this series of values that we wish to suggest a range of normal values, and a method of expressing the values that can be readily understood. We realize that our series of normals is small at present, and we plan to extend the number before finally publishing our results. The analytical data obtained for an enzyme represent the activity of the enzyme but not the enzyme itself, and it seems more logical here than elsewhere to arbitrarily take 100 as the normal. If one averages the findings for each of the three enzymes and assumes that this average is 100 per

cent, it is simple to calculate a factor by which all other values may be expressed in terms of 100 per cent. (As will be noted in Slide 6), the normal range of activities was found to be from 45 to 151 per cent for protease, 72 to 126 per cent for lipase and 56 to 169 per cent for amylase.

In a group of 11 cases suffering from miscellaneous gastro-intestinal disorders it was noted that a number gave slightly subnormal values, suggestive of reduced pancreatic activity.

The question has frequently been raised as to whether or not the external secretion of the pancreas was affected in diabetes. The most complete study in this regard was that by Jones, Castle, Mulholland and Bailey (8) in 1928. They studied 68 unselected diabetics and found the pancreatic enzymes diminished in nearly half the cases, the greatest alterations in enzyme activity being noted in the lipolytic and proteolytic ferments. On the other hand in the discussion of enzyme methods 4 years ago (2), Dr. Crohn stated with regard to this same problem: "My own experience is dimetrically opposite. I have always found increased pancreatic secretion in diabetes." We have made observations on 8 diabetics. Comparatively low values were obtained in 7 cases, the values for protease, being lower than those for lipase and amylase. On the other hand one case showed higher values than any we have observed in our normal group. It might be noted that most of these cases complained of abdominal distress.

Observations were made on four cases showing definitely low activities for all three enzymes. These were diagnosed as chronic pancreatitis, sprue, epigastric pain and severe diarrhea. In the fourth case the diagnosis was not clear. There can be no doubt about the reduced activity of the pancreatic ferments in these four cases. The average of the four cases showed the activity of the three enzymes in comparison to normal to be: protease, 19 per cent; amylase, 20 per cent; and lipase, 50 per cent.

Time does not permit a discussion of the relation of bile to enzyme activity, although it might be noted that in general a high bilirubin content and good enzyme activity appear to go hand in hand. However a few specimens were encountered with good enzyme activity in the absence of bile.

CONCLUSIONS

A system of enzyme analysis has been developed which permits an accurate estimation of the proteolytic, lipolytic and amylolytic activity of the enzymes of duodenal contents. When this system of analysis is applied to duodenal contents secured after stimulating pancreatic secretion with olive oil, it has been found possible to define the normal range of values with a reasonable degree of accuracy, and give these in terms of the normal taken as 100. Employing this method of recording the enzyme activities to pathological cases, abnormal values stand out very clearly from the normal. Very low values are found in pancreatitis and certain other conditions, while subnormal values are encountered in various gastro-intestinal disorders which may have an effect on the pancreas. In diabetes the enzyme activity may be subnormal, or considerably elevated.

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DISCUSSION

DR. ANDREW C. IVY (Chicago, Ill.): This is a piece of work which I personally have been very glad to find has been done by Dr. Myers and his colleagues. Before we can pass judgment on these methods, we shall have to use them ourselves and find out how accurate they are in our hands and how applicable they are as far as diagnosis is concerned.

We have many methods for enzyme determinations in the literature and some workers use some of the methods and other workers use others. As to whether Dr. Myers' methods will be suitable depends upon how we use them, and that will be the practical test of these methods: Will you use them?

DR. THOMAS R. BROWN (Baltimore, Md.): May I be permitted to ask Dr. Myers three questions?

In the first place, has he noted that the rise and fall of these three enzymes has always been parallel, as it were? Has he recognized the fact that most people feel this is true, and, therefore, would it be practical to determine only one of the three?

In the second place, has he done any work in comparison with these and comparative methods of quantitative estimates of enzymes in the stools?

In the third place, has he noticed, as I have done in work a good many years ago, there was often absence of these ferments in carcinoma of the head of the pancreas, while in certain cases of sprue and chronic pancreatitis, the figures are low?

In certain of my cases of sprue I had almost complete absence of them. I am singularly interested in his opinion of the first of these; in other words, do these ferments rise and fall together, or is there evidence that certain of these three rise and fall more than the others.

DR. HARRY SHAY (Philadelphia, Pa.): I should like to ask Dr. Myers how reproducible his results were on repeated occasions with the same patient. I wonder whether he noted that he obtained more closely reproducible results in his fractions after the olive oil stimulation than he was able to do in the fasting specimen.

The reason I bring this up is that I suspect that the latter may be the case. We have shown in our gastric motor studies that the effect of the tube through the duodenum does not influence gastric emptying. Because of this, the fasting specimen could be more frequently modified by gastric contents coming through the pylorus into the duodenum than would be the case after the addition of the olive oil to the duodenal contents, such an addition resulting in pyloric closure.

DR. VICTOR C. MYERS (Cleveland, Ohio): I wish to thank Dr. Ivy for his comment. With regard to the methods, we have used two methods in the case of protease and two in the case of lipase. I do not believe that if one uses the scheme of nomenclature that we employed—I do not know that I was able to say enough about this—it is going to make very much difference what method one uses, provided the method is properly carried out, and there is a straight-line relationship between the enzyme concentration and the end products formed.

I should like to repeat the statement about the scheme of nomenclature: "The analytical data obtained for an enzyme represent the activity of the enzyme but not the enzyme itself, and it seems more logical here than elsewhere to arbitrarily take 100 as the normal. If one averages the findings for each of the three enzymes and

assumes that this average is 100 per cent, it is simple to calculate a factor by which all other values may be expressed in terms of 100 per cent."

Now, as was noted on Slide G, to which I called your attention, the normal range of activities in the case of protease was found to vary between 45 and 151 per cent, between 72 and 126 per cent for lipase and between 56 and 169 per cent for amylase in our thirteen subjects. We hope to have a larger series of normals before we finally publish our observations.

It wouldn't make any difference, with this scheme of nomenclature, what method you used provided it was suited to the purpose. It seems to me this is a good way to express enzyme values because a medical man not so familiar with laboratory procedure can recognize 100 as a normal and deviations from the normal on this basis.

With regard to Dr. Brown's question, we did do fractional analyses and we do have simultaneous determinations, but it didn't seem practical to present all the observations at this time. The values for the three enzymes parallel each other fairly well, and if the duodenal con-

tents have a high content of bile (bilirubin) the agreement is quite good. However, the agreement between the three enzymes is not perfect. If one were to limit the determination to one enzyme, I would say to put protease first, amylase second, and lipase third. We have not done any determinations on stools. However, I would feel that work on duodenal contents was a great deal more definite and helpful than it would be on stools.

With regard to Dr. Shay's question, there is no doubt we get more constant values after the use of olive oil. Occasionally we have found the highest figure in the fasting specimen, but this is the case only infrequently. There is no doubt but what it is better to use the fluid collected after olive oil, since the enzyme concentrations are relatively more constant.

We have been hoping to get a better pancreatic stimulant and take one specimen after that stimulant and perhaps simply determine the protease on this specimen. However, the amylase and lipase estimations do give confirmatory and sometimes additional information.

The Triple Mechanism of the Chemical Phase of Gastric Secretion*

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THAT besides the first, or "nervous," phase of gastric secretion there is a second, or "chemical," phase, is evident from the fact that food substances or the products of their digestion, on introduction into the denervated stomach or into an isolated and denervated pyloric pouch, provoke secretion of the glands of the fundus and corpus of the stomach. The chemical phase again is divisible into two parts, the "pyloric" and the "intestinal," because the gastric glands may be stimulated by the introduction of food substances into the pyloric region of the stomach or into the small intestine.

I. THE PYLORIC CHEMICAL PHASE

More than thirty years ago Edkins (1906) claimed that under the influence of certain substances present in the food the pyloric mucosa elaborates a special and specific hormone, which provokes gastric secretion, and which came to be known as "gastrin." That such a hormone occurs is highly probable, but what its true nature may be is a matter of great controversy.

Some of the facts which seem to indicate that gastric secretion during the pyloric phase is under hormonal control are as follows: (1) The very limited absorptive power of the gastric mucosa. No proteoses, peptone, starch or fat are absorbed by the stomach. Only monosaccharides and amino-acids, *i.e.* substances which are very seldom or never present in the stomach, may pass through the gastric mucosa and enter the circulation (Delhouge, 1931). (2) Soap solutions and solutions of acetic acid, on being introduced into an isolated pyloric pouch elicit a copious gastric secretion from the stomach (Sawitsch and Zeljony, 1913). It is very doubtful that these substances as such are ever present in the blood. Moreover Zeljony (1912) showed

that the introduction of soap solution into the intestine, from where it may be absorbed, does not provoke secretion in the stomach when the latter is isolated from the duodenum. (3) The previous application of atropine or cocaine to the mucosa of a pyloric pouch prevents stimuli that are introduced into the pouch from exerting a secretory effect, presumably by delaying or preventing the formation of a gastric hormone. (4) Extracts of liver or meat provoke gastric secretion not only when injected intravenously but also when applied locally to the gastric mucosa. The minimal amount of liver extract necessary for the stimulation of gastric secretion by local application was found to be one-quarter of that required for the production of an equivalent secretion by intravenous injection (Kim and Ivy, 1933). This shows that the last-mentioned secretagogue produces its effect in some other way than through being absorbed.

It is not possible to discuss here the voluminous literature concerning the nature of the gastric secretory hormone. (Those interested in the problem may consult Babkin (1928) and Ivy 1930, 1931)). The results obtained by various investigators may be briefly summarized, as follows. One group of workers, as representative of whom may be quoted Luckhardt, Keeton, Koch *et al* (1915-1920), established the fact of the striking similarity between "gastrin bodies" and histamine, and expressed the view that these are similar and even perhaps identical chemical entities. According to them, the "gastrin bodies" can be extracted from the whole gastric mucosa and part of the intestinal mucosa, as well as from some other organs. A second group of investigators, who include Ivy and his co-workers (1932, 1937), are inclined to consider histamine as a gastric secretory hormone, having isolated it and identified it chemically. The other possibilities envisaged by these workers are either that

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there is no gastric hormone or that it has never been extracted from the pyloric mucosa. A third group, namely Rasenkow (1925) and his students, maintain that there is no gastric secretory hormone, but that the food substances or the products of their digestion act on the gastric glands directly after they are absorbed. Although this point of view is probably correct in respect of the action of the food substances in the small intestine, it does not apply, as was shown above, to the mechanism of the pyloric chemical phase of gastric secretion.

In view of this state of affairs Dr. S. A. Komarov of our laboratory was prompted to reinvestigate the "gastrin" problem. He approached it from another angle than did his predecessors. Instead of extracting the non-protein substance or substances from the pyloric mucosa and trying to eliminate the protein fraction as much as possible, he concentrated his efforts on isolation of that fraction, on the analogy that the powerful and indisputable hormone of the pancreatic gland—"secretin"—is a protein-like body, although differing markedly in composition from ordinary proteins. (Thus, for example, the crystalline secretin prepared by Hammarsten and his co-workers (cf. Agren, 1934) has a molecular weight of 5000, and gives a positive biuret, but a negative ninhydrin reaction. It is a body of basic character, and contains arginine and histidine but no cystine, tyrosine or tryptophan. According to Agren and Hammarsten (1937), it is digested by aminopeptidase).

Briefly Dr. Komarov's method consisted in the following. The mucous membrane of the pyloric part of the dog's or hog's stomach was boiled in 10 volumes of $n/10$ HCl and partially neutralized with $n/NaOH$ so that it remained only slightly acid to Congo. After cooling and centrifuging of the extract, the supernatant fluid was filtered through cotton wool and precipitated with 10 per cent crystalline trichloroacetic acid. A flocculent precipitate was formed. The whole was centrifuged and the precipitate washed three times with 40 to 50 volumes of 10 per cent solution of trichloroacetic acid in saline, twice with 50 volumes of acetone, once with benzene and twice with ether. It was then dried *in vacuo*. For intravenous injection such preparations were extracted with saline at 40° C. and rendered slightly acid with HCl or slightly alkaline with Na_2CO_3 . When tested biologically (Best and McHenry, 1930; Barsoum and Gaddum, 1935) they proved to be histamine-free. This method was based on the assumption that the pyloric mucous membrane, as mentioned above, may contain a substance similar in chemical properties to secretin, i.e. a heat-stable body, soluble in aqueous or saline solution having a slightly acid reaction, precipitable with trichloroacetic acid and insoluble in a large excess of acetone or ether. In other words, it was supposed that the pyloric hormone could be obtained by methods used with great success for the extraction of a vasodilating-free secretion from the intestinal mucosa (e.g. Still's crude secretin, cf. La Barre, 1936, p. 47 ff.). These suppositions proved to be correct. In all cases, i.e. in anesthetized cats or in unanesthetized dogs with permanent gastric fistulae, intravenous injection of the pyloric extract provoked secretion of gastric juice. In the latter case it did not produce any undesirable side-effects such as nausea, salivation, vomiting, movement of the bowel, etc. Even an amount of extract equivalent to 5 gm. of pyloric mucosa elicited a copious

gastric secretion. By means of repeated injections the secretion was prolonged in one of the experiments on an anesthetized cat for 5 hours. Injection of the extract did not lower the blood pressure, presumably because it contained no histamine or choline. Atropine did not abolish its secretory effect. Usually the pyloric extract produced a very small pancreatic secretion and increased the bile flow a little. The active property of the extract was chiefly contained in the pyloric mucosa, because fundic preparations did not provoke gastric secretion, though they had a slight secretory effect on the pancreas. Extracts of duodenal and jejunal mucosa produced a copious pancreatic secretion, but only the former evoked a secretory response from the gastric glands and that was but slight. The gastric juice secreted in response to the administration of the pyloric extract possessed high acidity and very low peptic power. This shows that the extract stimulated the parietal cells almost exclusively.

The finding that an active chemical body with almost specific secretagogue properties may be extracted from the pyloric mucosa is undoubtedly a step forward in our knowledge of the factors which possibly regulate gastric secretion during its pyloric chemical phase. However, we are not yet entitled to say that the substance extracted by Dr. Komarov from the pyloric mucosa is the hormone of this phase, because we are still ignorant of the mechanism of its liberation during gastric digestion and its transportation by the blood to the gastric glands.

II. SECRETAGOGUE EFFECT OF SOME FOOD SUBSTANCES, AND OF SOME OF THE PRODUCTS OF THEIR DIGESTION OBTAINED FROM THE SMALL INTESTINE

It was established long ago by Pavlov (see Babkin, 1928) that many different substances, when introduced through a fistula into the duodenum after it has been separated by operation from the stomach, provoke gastric secretion in dogs. The same effect is produced by feeding, in dogs with the stomach completely isolated and the esophagus connected with the duodenum (Frouin, 1922; Ivy, Lim and MacCarthy, 1925). This represents the so-called "intestinal phase" of gastric secretion. There are some indirect indications which seem to show that chemical substances, acting from the duodenum, stimulate the gastric glands not by liberation of a special hormone but after their absorption. For example, there is the fact of the very long (1- to 3-hour) latent period of gastric secretion when activated by such a method (Ivy, Lim and MacCarthy, 1925; Webster and Armour, 1932, and others), as well as the effect of atropine, which temporarily inhibits the gastric secretion but does not diminish its total volume (Webster and Armour, 1932). Many of the substances absorbed from the intestine stimulate the secretory cells of the secretory gland directly, but some of them are probably acting on the secretory cells through the local nervous plexuses.

Each of the three principal groups of food substances acts on the gastric glands in a different way.

(1) *Protein*. Peptone and hydrolysed protein act as secretagogues via the intestine. Subcutaneous injection of hydrolysed protein was ineffective. Those amino-acids which stimulate gastric secretion also act as secretagogues via the intestine (for literature, see

Ivy, 1930, and Cowgill and Smith, 1933). The extractive substances of meat, when introduced into the duodenum or the small intestine, provoke gastric secretion. It is not known, however, exactly what fraction of the extractive substances exerts the secretagogue effect (*cf.* Babkin, 1928, p. 255). Among the nitrogenous bases contained in extracts of fish muscle, it was found that the arginine-histidine and lysine fractions exerted a secretagogue effect. The effect of the former fraction was much stronger than that of the latter. Since the nitrogenous bases were introduced into the stomach, it is not known exactly from what part of the gastro-intestinal tract they acted (experiments of J. Campbell—see Babkin, 1934). A number of amines which may be formed in the intestine from amino-acids stimulate gastric secretion (Ivy and Javois, 1925).

(2) *Fat.* It is well known that the action of fat on the gastric glands has two phases: an inhibitory and an excitatory. During the inhibitory phase the nervous mechanism of gastric secretion is chiefly affected, so that under certain conditions a dissociation of the functional properties of the gastric glands may be achieved (Alley, MacKenzie and Webster, 1934). Thus the production of the fluid and acid of the gastric juice in certain cases may be diminished very little, while its peptic power is greatly reduced. From a practical point of view it is important to note that a diet rich in fat, administered over relatively long periods of time, may induce a hyper-secretory condition of the gastric glands, coupled with almost complete paralysis of the vagal "trophic" action. In experiments carried out in this connection on a dog, fat was introduced directly into the duodenum, which had been separated from the stomach (Alley, MacKenzie and Webster, 1934).

(3) *Carbohydrate.* Glucose solutions, on introduction into the stomach, elicit a very scanty secretion of gastric juice. When added to other stimuli glucose greatly increases the concentration and total output of pepsin, although the volume of the secretion is somewhat diminished. The increased discharge of pepsin under the influence of glucose is especially noticeable when the effect of glucose is combined with the secretagogue effect of alcohol (experiments of Dr. M. H. Friedman, in this laboratory). Alcohol is a stimulus which activates a flow of gastric juice extremely poor in pepsin. When the special effect of glucose (60 gm. of glucose in 200 cc. of water administered by mouth to a dog with a Heidenhain pouch) was added to the secretagogue effect of alcohol (200 cc. of 5 p.c. ethyl alcohol given per rectum), the concentration and total output of pepsin rose considerably.

Choline and lecithin. Since choline and lecithin are widely distributed in food stuffs, their effect on the secretory activity of the gastric glands is of special interest. It was known that the introduction of choline into the gastro-intestinal tract stimulates gastric secretion (Ivy and Javois, 1925). In our laboratory Dr. MacIntosh and Dr. Krueger (1938) analyzed the effect of choline as well as that of lecithin in this respect. Choline, when introduced into the stomach in comparatively large doses (0.5 to 1.0 gm. in 50 cc. of water) evokes a scanty secretion of gastric juice of very low acidity but very rich in pepsin. The latent period of the secretion was about one hour, which

indicates that the substance acted not from the stomach but from the intestine. A dose of 6 gm. of lecithin, which is equivalent to 1 gm. of choline, produced an effect in all respects analogous to that of choline. The latent period of the gastric secretion was, however, twice as long as in the case of choline, which was evidently due to the time required for the liberation of choline from lecithin in the intestine. On choline or lecithin being added, the secretory response to a standard meal was increased. This augmentation of the secretion after a single dose of choline lasted for two to three days, gradually diminishing. Therefore this was the result not simply of a summation of the secretagogue effects exerted by choline and food substances, but of an increased excitability of the gastric glands. The average augmentation of the volume of the gastric secretion, after the preliminary introduction into the stomach of 1 gm. of choline and 6 mg. of lecithin respectively, was on a standard meal of meat 84 per cent and 44 per cent, on butter 130 per cent and 140 per cent. There was, however, no increase in the volume of the gastric secretion on a standard meal of white bread after lecithin administration. The output of pepsin was not essentially increased in these experiments.

The data of MacIntosh and Krueger are of great importance from the dietetic standpoint. Although in the various tissues, *e.g.*, in muscle, there is only a small amount of free choline, the total amount of choline is rather great. Thus liver contains 2300 mg. per Kg., beef muscle 760 mg. per Kg., pancreas 2300 mg. per Kg., and so on (Fletcher, Best and Solandt, 1935). This choline is quickly liberated by post-mortem autolysis, and may be present in commercial meats. Lecithin, when hydrolysed by the digestive ferments, liberates choline (Bergell, 1901), and hence may act on the gastric glands in the form of choline.

The presence of choline in food substances first of all may possibly provide a partial explanation of the well known fact that the gastric juice of the second phase of gastric secretion is richer in pepsin than that obtained through the administration of histamine or "gastrin," which stimulate almost exclusively the parietal cells. Another important fact that may perhaps be explained by the presence of choline in different food substances is the varied response of the gastric glands of one and the same animal at different times to a standard test meal. By means of special diets it is possible to raise or lower the general excitability of the gastric secretory apparatus, so that the same food will produce a different secretory effect. In this connection the experiments performed in Professor I. P. Rasenkov's laboratory may be quoted (Koschtojan, 1929; Iwanow, 1929, Tschebischewa, 1929). The effects of various alimentary regimes of long (30 to 60 days) duration on the response of the gastric glands to standard test meals, were studied in dogs equipped with a Heidenhain or a Pavlov pouch. The dogs were placed respectively on diets of meat, carbohydrate (cabbage soup, potatoes, dark bread, salt), fat (butter and dark bread), milk and bread, or mixed food. It was found that the response of the gastric glands to standard test meals of meat, bread or milk was $1\frac{1}{2}$ to 3 times greater when the animals had been on a meat or fat-containing diet than when they had been on a predominantly carbohydrate diet.

Thus it was shown that by the selection of a suitable diet the secretory activity of the gastric glands could be influenced.

III. DIRECT EFFECTS OF HYPOGLYCEMIA AND OF CERTAIN SUBSTANCES IN THE CIRCULATING BLOOD ON THE VAGAL SECRETORY CENTER

After somewhat contradictory initial reports on the effect of insulin on gastric secretion, it was finally established in experimental animals and in man that subcutaneous, intramuscular or intravenous administration of insulin provokes secretion of gastric juice. (For reviews of the literature, see Roholm, 1930; Ivy, 1930; La Barre and de Cespédès, 1931 a; Boldyreff and Stewart, 1932 a and b; Okada *et al.*, 1929, 1930, 1933; Welin and Frisk, 1936, and others). 45 to 60 minutes after intravenous injection of 2 to 10 units of insulin in a dog, or 12 to 20 units in a man, gastric secretion appears or if it is in progress is increased. In such cases, the onset of gastric secretion in man coincides with a slight general insulin reaction and with a fall of the blood sugar concentration, which in different subjects may be reduced to between 34 and 68 mg. per cent (Roholm, 1930; Welin and Frisk, 1936). Intravenous injection of a strong solution of glucose in various quantities in the dog or in man prevents or arrests the effect of insulin (Roholm, 1930; La Barre and de Cespédès, 1931 b; Okada, 1933). The statement of Boldyreff and Stewart (1932 b) to the contrary is not convincing, because the amount of glucose (15 cc. of 20 per cent solution) by intravenous injection of which they attempted to counteract the secretory effect of insulin was probably not sufficient to raise the blood sugar concentration in their animals (see Table II of their paper). In cases of diabetes where the blood sugar is high insulin is ineffective, but if the blood sugar is lowered sufficiently by a therapeutic dose of insulin adequate for a given patient, an additional dose of insulin will lower the blood sugar below the normal level and provoke gastric secretion (Meyer, 1930). Therefore, Roholm (1930) was justified in considering the gastric secretion elicited by insulin as a hypoglycemic symptom, produced by the fall of the blood sugar concentration.

The amount of gastric juice secreted by the human gastric glands in response to insulin administration varies between 100 and 200 cc. Its free and total acidities and its concentration of total chloride are high (Welin and Frisk, 1936). The pepsin concentration of "insulin" gastric juice in the dog and in man is high (Roholm, 1930; Boldyreff and Stewart, 1932 b; Dr. D. R. Webster in our laboratory—unpublished results). Much more mucus is secreted by the stomach of man after insulin, than after histamine administration (Welin and Frisk, 1936). Atropine abolishes the secretion provoked by insulin. Section of the vagus nerves also abolishes the secretagogue action of insulin, whereas it does not prevent histamine from producing its usual effect (Okada *et al.*, 1929; La Barre and de Cespédès, 1931 c, Webster—unpublished results). All these data indicate that insulin, or rather a hypoglycemic state of the blood, stimulates not the peripheral parts of the gastric secretory apparatus, but the centers of the parasympathetic system in the brain. La Barre and de Cespédès (1931 d), in fact, demonstrated this by means of the cross-circulation method of Heymans, using two dogs.

One dog, which was equipped with a gastric fistula, and the head of which was connected with the rest of its body only by the vagus nerves in the neck, received blood from another dog. Injection of insulin in the latter, which resulted in hypoglycemia, provoked the secretion of a highly acid gastric juice in the former.

Although the reduction in the blood-sugar concentration which follows insulin administration, while sufficient to provoke gastric secretion, may be not at all great, reaching approximately 68 mg. per cent (Welin and Frisk, 1936), it can hardly occur in quite normal persons. However, such conditions have been observed in cases of hypoglycemia of spontaneous type, so-called hyperinsulinemia, as reported by some clinicians (*cf.* Harris, 1935). Again, injection of a large amount of glucose, resulting in a state of hyperglycemia, may be followed by a reactive hypoglycemia, where the blood sugar is sometimes as low as 59 to 53 mg. per cent (Okada *et al.*, 1929).

Another example of stimulation of the vagal secretory center by substances circulating in the blood may be seen in the effect of amino-acids (Okada, 1930, 1933; La Barre and Destrée, 1935 a, b and c). Okada and his co-workers showed that intravenous injection or intraduodenal administration of large doses of glycocoll, alanin, glutamic acid, histidine or glycylglycine provoke gastric secretion in the dog and in man. After intravenous injection of amino-acids a marked rise of amino-acid nitrogen takes place in the blood, usually coupled with a fall in the blood sugar concentration of varying degree. After intraduodenal administration of glycocoll in man the former phenomenon was observed, whereas the latter did not occur; nevertheless the volume of the gastric secretion increased and its free and total acidities rose.

The secretion provoked by amino-acid could be arrested by administration of atropine or glucose. No gastric secretion could be elicited by means of amino-acid in dogs with the vagus nerves cut in the chest above the diaphragm (Okada *et al.*, 1930) or at the cardia (La Barre and Destrée, 1935 e). Therefore all these facts show that the amino-acids provoke gastric secretion by stimulating the parasympathetic secretory centers in the brain.

La Barre and Destrée (1935 a, b and c), who confirmed the results obtained by Okada *et al.* on dogs, believe that the secretagogue effect of amino-acids is due to the concomitant hypoglycemia. However, it would seem that the amino-acids are able to stimulate gastric secretion directly, although in the experiments in which they were injected intravenously their secretagogue effect undoubtedly was coupled with that of hypoglycemia. This is evident from the fact that the intraduodenal administration of glycocoll in man elicited a flow of gastric juice but did not alter the blood sugar concentration. Moreover La Barre and Destrée (1935 c) themselves observed that the secretion of gastric juice begins before any significant fall in the blood sugar concentration takes place (*e.g.* before the blood sugar level, which had been 92 mg. per cent before the injection, had fallen below 82 or 78 mg. per cent. Further experiments are necessary in order to settle this question finally).

Facts discussed in this section show that during the second or chemical phase of gastric secretion, the vagal secretory center may be stimulated, not reflexly as in the first phase, but directly by appropriate

changes in the composition of the blood. The participation of the parasympathetic secretory innervation also explains why the concentration of pepsin is higher in the gastric secretion of the chemical phase than in that obtained after histamine administration.

CONCLUSIONS

Gastric secretion during its chemical phase is regulated by a triple mechanism: (1) A pyloric hormone, probably "gastrin," acts directly on the gastric glands. (2) Certain food substances, or some products formed or liberated by them, stimulate the gastric glands after being absorbed by the intestine. (3) Some of the absorbed products of digestion, as well as a hypoglycemic state of the blood, act on the vagal centers in the brain.

The effects produced by the stimulants of the chemical phase are manifold: some of them stimulate chiefly the parietal cells, others almost exclusively the peptic cells, and some of them in addition are able to alter the excitability of the gastric glands and so to modify the response of these glands to other stimuli. The fact that there are present in food various secretagogues, which act on different parts of the neuroglandular apparatus of the stomach, is of great importance in the selection of diets for patients with different ailments of the gastro-intestinal tract, as well as for normal persons.

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DISCUSSION

DR. HEINRICH NECHELES (Chicago, Ill.): The more we learn about the mechanism of gastric secretion, the more complex it becomes.

So far as we can see from our own investigations, there are two mechanisms which regulate the secretion of the stomach. The one is a stimulating one, and the other an inhibitory one. The stimulating one, I think, we can divide into the neurogenic and the humoral, the humoral being provoked by metabolites, absorption products and possibly hormones. The inhibitory is still very little known, but we think at least two substances must be considered. The one is enterogastrone and the other one is contained in the posterior lobe of the pituitary.

We have recently found that stimulation of the central vagi antagonizes the effects of acetylcholine in the body more or less completely and this may be a true reflex. Since effects of vagus stimulation are more or less due to acetylcholine, there may be a new physiological antagonism in the inhibition of gastric secretion.

The other substance that inhibits gastric secretion is enterogastrone, a substance which has been extracted from the small intestine by Ivy and Lim. We have recently found a similar substance in the urine of normal persons, while the urine of patients with peptic ulcers seemed to contain less of it.

There must be a very fine balance between these stimulating and inhibitory substances which, when disturbed, will be followed by more or less pathological changes in the secretion (and motility) of the stomach.

DR. SAMUEL MORRISON (Baltimore, Md.): There is another secretion in the stomach to which attention should be called. That secretion is the intrinsic factor of Castle. The question has arisen concerning whether this secretion is affected by the pyloric or pyloro-duodenal hormone, and I should like to take this opportunity to ask Dr. Babkin to discuss that phase; for example, the very tissues which have anti-anæmic potency are exactly those which give rise to the pyloric or pyloro-duodenal hormone, and it seems plausible to consider that the mechanism in one case may apply to the other.

It is also said that the pyloro-duodenal tissues as used in the treatment of pernicious anemia act in the nature of replacement therapy, but there is reason to believe, and evidence to substantiate the belief that the action is one of a pyloro-duodenal hormone rather than replacement therapy.

The question always arises as to whether a pyloric hormone exists. Dr. Babkin has pointed out that there is such a specific hormone and that it is probably not histamine. If we take a broader conception of the pyloro-duodenal hormone as we have been led to do from our studies, it is possible to consider it a hormone which stimulates more than one gastric secretion. It has been suggested by certain investigators that histamine is the pyloric hormone. This does not square with the newer evidence at hand as Dr. Babkin and others have shown. Histamine stimulates acid secretion, and perhaps ferments also, but it is an accepted fact that it does not increase the secretion of intrinsic factor. A gastric hormone which has this property must therefore be something other than histamine or something in combination with histamine. In other words, it must be a composite hormone of which histamine may form only one constituent part.

DR. ANDREW C. IVY (Chicago, Ill.): I don't agree with Dr. Necheles when he states that physiological investigations are making the process for the secretion of gastric juice more complex. I insist that these investigations are making this process more simple. We are explaining a mysterious process by discovering several

factors, and when we make such discoveries, or when we take the mystery out of a process, we make the process simple.

Also I do not like the latter part of the discussion of the last speaker, because he states that histamine can't be the gastric hormone simply because it causes the formation of acid alone. He sets up a picture of what he thinks should be the gastric hormone, that it should be something that stimulates both acid and pepsin. I wonder how he can be so sure what kind of hormone the intestinal lining should form to stimulate the gastric gland.

We are not making hormones. We are not making this body work as we think it should work. We are trying to find out how it works.

DR. PHILIP W. BROWN (Rochester, Minn.): We talk about the influence of ingested foods on the gastric secretion, and I have been particularly interested in the factors of foods ingested in relation to nutrition of the body as a whole, and I wonder if there is any relationship at all between the vitamins and these hormones, whether in the B complex or in any of the other mysterious letters of the alphabet. I don't know; I am just asking.

DR. CHARLES W. LUEDERS (Philadelphia, Pa.): "In my studies in 1930-1931 on the effect of Insulin upon external pancreatic secretion, a search through the literature confirmed the finding by himself and numerous investigators: that Insulin stimulates Gastric secretion and Acidity. I would like to ask Dr. Babkin if he has ever studied the effect of the intravenous injection of amino-acids and of fatty acids upon gastric secretion and Acidity, work reported by other investigators; confirming the clinical results following diets rich in these two classes of food elements."

DR. ASHER WINKELSTEIN (New York, N. Y.): I wish to congratulate Dr. Babkin on a further clarification of a very confusing problem, the chemical phase of gastric secretion.

In the presentation we will give this afternoon, we will emphasize the importance of the vagus nerve. It is therefore interesting to hear Prof. Babkin stress the vagus nerve factor in the ulcer problem. At the Mt. Sinai Hospital, the diabetic and gastro-enterological clinics are neighbors. The diabetic clinic has an enormous number of patients. We have several hundred to a thousand

patients with ulcer in the gastro-intestinal clinic. My experience in fifteen years is that the number of patients with diabetes mellitus who have peptic ulcer is extremely small; as a matter of fact, in our experience it is less than the fingers of two hands, over a period of many years, and we have always wondered about that.

It is possible that the hunger mechanism which Dr. Babkin described today may play a role in the symptomatology of ulcer in explaining the hunger pains. It may also play a role in the hypersecretion of ulcer. If it is eventually shown that the hypersecretion of ulcer in some patients depends on a hypoglycemia due to excessive insulinism, that may be the explanation of the antagonism between diabetes mellitus and peptic ulcer. It may even be (although the suggestion is a bit fanciful) that ulcer may prove to be a pancreatic or adrenal disease.

DR. BORIS P. BABKIN (Montreal, Canada, closing the discussion): First of all, speaking about "gastrin," I would like to emphasize that we must be very careful in stating that "gastrin" is a hormone which stimulates the gastric glands during the second phase, because it may be one of those substances, like histamine or choline, which may be extracted from the gastric mucosa and which are also able to stimulate the gastric secretion. Therefore we are not yet entitled to say that the substance extracted by us from the pyloric mucosa and which we called provisionally, "gastrin" is a hormone. There must be some other physiological proofs, which we have not yet obtained, that the extracted substance really plays the part of a hormone. As far as histamine is concerned, I do not think that it is a hormone of the second phase of the gastric secretion. This does not mean that histamine has to be excluded altogether from the picture. I am convinced, for instance, that histamine plays a part during the first or nervous phase of gastric secretion. According to our investigations, histamine stimulates the parietal cells by passing through them, and appears in the gastric juice. I do not think I can answer the question about the Castle's intrinsic factor because I never worked on this problem. A colleague asked me about the effect on gastric secretion of amino-acids and fatty acids. We have the necessary dogs with fistula and pouches and we intend to try on them the effect of these substances. As regards the effect of insulin on gastric ulcer in man, I must admit that I am unable to answer this question.

The Present Status of Treatment in Chronic Gastritis: Gastroscopic Observations

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AMERICAN clinicians have been reluctant to accept chronic gastritis as a clinical entity; and during the past few decades the completely accepted conception of gastritis in Europe has here met considerable healthy skepticism. This may be rightly so, for many have found the very wise old adage: "Be not the first to lay aside the old nor the last to accept the new."

Moreover, it should not be forgotten that even one hundred years ago there took place a lively debate between Robert Carswell (1) and Broussais and Louis on the gastritis question. The English Carswell at-

tempted at that time to prove that the pathological demonstrations of Louis and Broussais of the French school, regarding the entity gastritis were erroneous. In sharp contrast is the present recognition of gastritis by the English school, headed by Sir Arthur Hurst and many others. They even believe, as do Faber (2) and Konjetzny (3), that chronic gastritis is a forerunner of gastric carcinoma, pernicious anemia, subacute combined degeneration of the cord and even peptic ulcer (4).

There has also been a similar complete reversal of

opinion by many observers in this country. For example some observers at the Mayo Clinic, like Waltman Walters and Sebenning (5) in 1931, believed that chronic gastritis in the absence of pyloric obstruction did not occur, and stressed the geographical factor of gastritis. They felt that the gastritis seen in Europe was not seen in America. Although Konjetzny, Orator, Puhl and other European investigators have offered pathological case evidence that gastritis is the precursor of gastric carcinoma, Comfort and Butsch (6) at the Mayo's just recently have been the first to our knowledge to demonstrate case records and pathological evidence in which gastritis preceded gastric cancer. A complete change of opinion at the Mayo group is now evidenced by independent reports on gastritis cases by Comfort (7), by Phil Brown (8) and the discussion by Eusterman (9) on Chronic Gastritis in the recent textbook by Eusterman and Balfour "The Stomach and Duodenum." At Johns Hopkins, Gaither and Borland (10) and Freeman (11) have similarly studied gastritis both gastroscopically and pathologically. Even if the gastritis—cancer claim is true in only a minor percentage of cases, proper therapeutic management of gastritis immediately assumes prime significance in the prevention of cancer.

One of the side-effects of the controversy has been that practically all observations have been limited to considerations of the actual existence of gastritis and its diagnosis. One is therefore struck by not being able to find any extensive American observations on the treatment of gastritis, under the direct control of gastroscopic visualization of the stomach and its response to therapy. The few gastroscopic observations on medical therapy of gastritis are mainly the brief ones made by Schindler in his recent textbook (12); the pernicious anemia studies of Jones and Benedict (13); the secondary anemia studies of the French authors Francois Moutier and Paul Chevalier (14); the allergic studies made by Rene Chevallier (15) of Lyons; and isolated case reports. Generally, the European discussors of therapy have focussed largely on the advisability of sub-total gastrectomy; and European physicians and surgeons are still engaged in active controversy on this moot question.

Among related considerations have been the etiology of gastritis and the pathogenesis principally involving gastritis as the possible precursor of peptic ulcer and gastric carcinoma. Numerous contributions have been made recently on the roentgen relief diagnosis of gastritis and one experienced observer—Jacob Buckstein at Bellevue Hospital (16) has gone so far as to claim that the diagnosis of duodenal ulcer can often be materially aided by the roentgen-relief diagnosis of the associated hypertrophic gastritis. Ross Golden has recently similarly described the differential diagnosis of antral gastritis and antral carcinoma and discussed the inherent diagnostic difficulties (17). However, it has been our experience—as in Schindler's that in the majority of cases the roentgen ray diagnosis of gastritis is unreliable since it usually is not corroborated by direct visualization through the gastroscope. It cannot be denied however that the hypertrophic variety of gastritis can often be detected roentgenologically by the mucosal pattern relief, particularly in experienced hands.

Before considering the therapy of gastritis it is important to understand the problem of classification.

All references herein are directed to the chronic form of gastritis and in certain instances the subacute form. No study has been made of the acute form of gastritis which is transient and passing. There is no doubt but that Schindler's classification of gastritis is the simplest and easiest to work with; viz.—atrophic, hypertrophic, superficial and the post-operative forms. However it cannot be forgotten as Chevalier Jackson (18) has pointed out, that it is not comprehensive. After over 35 years of gastroscopic inspection of the stomach Jackson felt that Schindler's classification of gastritis into four groups was not complete and stated that as many as 30 varieties of gastritis require recognition, particularly as significant of the subsequent changes, pathogenesis and development into disease. It was for this reason that we adhered originally (19) to Moutier's classification based on gastroscopic and pathologic structural changes. However to simplify and clarify the issue, we will combine both Schindler's and Moutier's classifications, and attempt simple, concise and yet descriptive terms, such as "atrophic gastritis with erosive features," or "ulcerative gastritis with congestion," or "mixed gastritis" of hypertrophic and atrophic varieties with edema, etc.

Our gastroscopically controlled studies of gastritis therapy embrace from 600-700 gastroscopies. Conclusion as to results were made only if the following criteria were observed in the patients studied for this presentation:

(a) Patients were gastroscoped at least twice (and in some cases as often as eleven times). (b) Patients only were used who had been followed in clinic and private practice regularly and were cooperative. (c) X-ray and biliary studies were negative and extra-gastric pathology was absent. (d) Observations were made in patients followed for a minimum of one year, a maximum of 5 being attained in some. However several exceptions were made in the subacute variety. (e) Patients who had been checked by more than one gastroscopist by the authors and Dr. Chevalier L. Jackson. (f) Routine laboratory studies were made including Wassermans, urines, complete blood counts, gastric analysis, biliary drainage, etc., and various special tests as Gruskin-carcinoma, basal metabolism rate, etc., included.

We therefore enclose the results of our observations according to the English custom as exemplified by Hurst's studies in a small group of cases are carried out. Because of the above criteria a large number of cases was weeded out and a mass statistical report involving several hundred cases was thus avoided. It is felt that better conclusions can thus be reached and hence a small group of each variety is thus presented, each case exemplifying a special point.

We can declare the following opinion at the outset and cite case records in proof:

(1) The atrophic form of gastritis in the absence of primary or secondary anemia has not shown regeneration or return to a normal mucosa in our experience. It has been our custom to grade the atrophies into three grades, from pallor to complete thinning out of the mucosa, effacement of the rugae and blanching. We have not even seen lessening of the pallor in these non-anemic cases. It appears that the mucosa does not regenerate again in these cases under present methods of therapy. We have been interested in the observations of Moutier, Chevallier (20), etc., to the

effect that anemias can be expressed not only in blood changes but also by atrophic gastritis in the absence of blood changes. That is to say, it can be possible for non-anemic anemias to occur just as aleukemic leukemia. They report that their cases of atrophic gastritis anemias without blood changes respond to liver therapy and improve symptomatically. We cannot verify this as yet since we have not had adequate time to check this recent observation. We cannot subscribe to Schindler's belief that atrophic cases should "especially avoid milk, since it invariably causes gas and belching" (21). Not only is this not noticed in pernicious anemia cases where an extensive and severe atrophic gastritis is present but we have not observed this reaction as a general rule in the non-anemia atrophic gastritis. The achlorhydria to histamine that some of these cases present, similarly has not returned to normal despite hydrogen peroxide lavages. This does not corroborate Hurst's and Darling's observations on the return of histamine achlorhydrias in the atrophic gastritis cases under hydrogen peroxide lavages. Our conclusion is rather in agreement with Bockus, Monaghan, et al (22) that improvement but not restoration of acidity occurs. It should be recalled that Hurst's and Darling's and Hartfall's diagnosis of atrophic gastritis were made by gastric analysis and not by direct inspection of the stomach by the gastroscope. Jones and Benedict have shown that pernicious anemia types of atrophic gastritis will have a restoration to a normal appearing gastric mucosa under liver therapy (13).

(2) The congestive, the hemorrhagic or erosive, the ulcerative, the edematous forms of gastritis, whether in subacute or chronic form can and do respond to treatment. These forms are quite frequently associated with the etiologic factors outlined in (1) under therapy, such as upon the removal of offending causative factors these forms will often show a prompt response.

(3) The superficial, catarrhal or mucorrheal form of gastritis responds similarly to therapy but requires that certain implicated mechanical irritant factors be eliminated or ameliorated as in sinus disease especially with purulent discharge (which we see to a great extent in the Philadelphia climate), post-nasal discharge ("drip"), oral sepsis, etc.

(4) The hypertrophic forms per se do not respond to therapy. Symptoms may be absent, yet this form persists and seems particularly susceptible to ease of remissions in symptoms. We have observed only one case in which a transition has occurred from the hypertrophic to the atrophic variety. This is in contrast to the claims by various observers and pathologists (23), with the exception of Schindler.

(5) The post-operative form of gastritis does not respond to therapy although symptoms may be absent.

(6) The mixed types will show improvement on therapy as to congestive, ulcerative, edematous or mucorrheal forms but hypertrophic and non-anemic atrophic features show no therapeutic response throughout and are refractory to all treatment.

We have found in certain instances where the ulcer management with alkalis in forms of gastritis has failed that antacid non-adsorbed substances such as colloidal kaolin in alumina gel or alumina gel alone will prove effective in ameliorating symptoms. This supports Brown and Eusterman's independent observations at the Mayo Clinic. Attempts at medication

adjustment can at the present time be made only empirically. The indications for the use of alkalis or adsorbent demulcent, at present cannot be foreseen as to the type of case in which the one or other should be selected. However, it may be presumed that a more judicious use is made of medication of a more "soothing," demulcent and antacid type inasmuch as we have observed gastroscopically that certain preparations can remain in contact with the gastric mucosa for an hour to two hours.

The so-called pigmented spots seen by the gastroscopists are probably old submucosal or mucosal hemorrhage. We have observed that in those cases where general increase in vitamins is included in the dietary and medication there is a tendency to regression or frequently disappearance. It is impossible to state definitely whether these may have been due to vitamin C deficiency in some cases, as indicative of friability, capillary hemorrhages, etc.

Every gastric post-operative case whose stomach was inspected had definite and often marked evidence of a gastritis. However this does not necessarily imply that these stomachs cause symptoms. They may and they may not. The presence of symptoms in gastritis may depend on involvement not only of an inflamed mucosa but also upon encroachment on submucosal layers where the rich nerve supply is. Thus an inflamed mucosa may indirectly cause pylorospasm or gastric spasm with result in pain or pain-equivalent sensations. It may be that these symptoms are caused by nerve involvement in the gastric submucosa with subsequent pain, distress or equivalents. Or the factor of an inflamed mucosa may be responsible for other types of disturbances—not necessarily painful, but causing gassy distress, anorexia, weakness, symptoms due to disturbances in secretion, etc. Faber, Mays, Moutier and others have shown the frequency of submucosal hemorrhages; edema and infiltrations in these gastritis cases, demonstrating that many of them have more than superficial mucosal involvement. There has been pathological evidence also of the fact that the pathology of certain of the gastritis cases originates in the submucosa. This is analogous to the demonstration by Lewis Gregory Cole (24) who has shown that gastric ulcer may originate as a "boil" like lesion in the submucosa first, with extension up into the mucosa. Moutier has even demonstrated pathologically that the nerve changes are extremely frequent in all forms of gastritis (25).

The sympathetic ganglia as well, he demonstrates, are damaged—involving the plexuses of Auerbach and Meissner. V. Orater, L.d' Amata and P. Mairi have independently shown the same findings pathologically. Confirmatory observations on this nerve affection in gastritis are lacking probably due to the fact that special nerve tissue stains are not used in pathological examinations, as the above investigators have done. These points are raised because of their therapeutic considerations on the claim of some observers regarding underlying autonomic nerve imbalance factors, besides the disturbances in secretion and motility under nerve control.

For example M. Pevsner and O. Gordon (26) have studied 500 cases of gastritis, diagnosed as such by the cytologic study of the sediment as described by Badilkes and by Glaessner. This technique is along similar lines as that reported by Monaghan, Bockus,

Kornblum and Moffat before this Society last year. Pevsner and Gordon emphasized the fundamental factor of neuro-vegetative system imbalance and reported better results when patients were placed on concentrated calcium therapy. This concept of vegetative nerve imbalance may receive some support by virtue of the fact that many of these patients are nervous, irritable, weak, neurasthenic, easily exhausted, or depressed. The question may therefore be asked if it is possible to consider a so-called mucous colitis or unstable colon or peptic ulcer on a neurogenic etiology can it likewise be possible to have a gastritis with neurogenic factors since many of these patients are subjected to as much psychic stress and strain as the peptic ulcer or unstable or so-called "mucous colitis" patients? It is impossible to conclusively answer any of these questions but the clinician handling gastro-intestinal problems cannot help but be impressed by the great psychological factors playing a dominating role in the symptoms of the above conditions and how necessary it is to ameliorate the psychic disturbances in successful therapy.

In the superficial form of gastritis where there is excessive mucus, Schindler and others state that lavage should be carried out every morning over a long time until repeated gastroscopic examinations show the absence of all pathological changes. This has been obviously not feasible as a routine procedure particularly since the superficial forms of gastritis are so common in occurrence. We have met with favorable results in the therapy described below. Schindler states that drugs are not necessary and act as irritants. We have found that alkali preparations, particularly adsorbent ones in the gel forms, are most useful in the removal of mucus, as a local mechanical sedative and in forming a soothing coating over the inflamed or irritable gastric mucosa.

At the present time our present method of therapy in chronic gastritis can be summarized as follows:

(1) Removal of all possible etiologic factors as:

(a) Foci of infection in mouth (oral sepsis), teeth, gums, tonsils, nasal accessory sinuses, etc. (b) Indiction of smoking and alcoholic beverages. (c) Faulty habits of hygiene, inadequate mastication, irregularity of meal-time, food bolting, chronic dietary indiscretions, possibly food allergy, etc. (d) Reflex and contiguous pathology as duodenal disease (ulcer, parasites, etc.), gall-tract disease (infection, inflammation, etc., with continued biliary regurgitation). (e) Correction of autonomic nerve imbalance and psychological abnormalities.

(2) Bland diet, nutritious and emphasizing small frequent feedings.

(a) The atrophic, achlorhydric forms may add seasoning to food, to increase appetite, gastric secretions and weight. (b) The hypertrophic forms involving the ulcerative and erosive varieties should be managed as peptic ulcer cases with bed rest.

(3) Medication varies with degree of acidity, e.g. dilute hydrochloric acid—U.S.P. is given in the atrophic and achlorhydric forms, whereas antacid adsorbents or alkali powders with minimal absorbability are indicated in hyperacidity. Included are vitamins (especially B, B₂, and C (Cevitamic Acid) in all erosive and hemorrhagic types, colloidal kaolin with aluminum hydroxide, antispasmodics (tr. belladonna,

atropine, etc.), iron (ferrous sulphate preferably), sedatives (phenobarbital, bromides), digestants as pepsin, etc.

(4) Gastric lavages, twice and three times weekly in achlorhydric and marked hypochlorhydric types. Excessive mucus, regurgitated bile, retained secretions, etc., are thus removed, avoiding irritant effects and a return to function of the acid-secreting glands may be thus accomplished. Hydrogen peroxide—one-half to one ounce to the pint of warm water is best. The weak silver solutions may be used, but the danger of argyria must be borne in mind.

(5) Spa waters, as Vichy, Kalak, Carlsbad, Saratoga Springs, etc., for their lavaging effect and mineral content.

(6) Physical therapy—local heat by baking, moist applications, diathermy, all for pain (High voltage X-ray for intractable hypertrophic forms still in experimental stages).

(7) Surgery to be used only in very severe and intractable cases with severe ulcerative and chronic hemorrhagic features. Post-operative inflammatory reactions locally, however, must be expected.

(8) Prophylaxis—the possible development into peptic ulcer, gastric carcinoma, or pernicious anemia in some forms, indicates that the principle of periodic health examinations should specifically be applied in these cases. Hence gastroscopic examinations and X-ray studies should be repeated at stated intervals, depending on the financial circumstances of the patients. Preventative medicine here is all-important.

In the large series of gastritis cases which we have treated during the past four years, it becomes apparent that although these therapeutic measures may frequently give very satisfactory results, these measures are entirely inadequate in the non-anemic and the hypertrophic forms, and in certain of the erosive as well. Here is a significant and important field of investigation and also of preventive medicine if it is possible that the hypertrophic and atrophic forms are among the precursors of gastric carcinoma, ulcer, pernicious anemia, etc., as so many observers believe and as growing evidence would appear to suggest.

The following groups rather than a large statistical series are presented in order to bring out facts concerning the forms of gastritis including their pathogenesis, response to therapy, course, and instructive features.

ILLUSTRATIVE CASE ABSTRACTS SUPERFICIAL, CATARRHAL OR MUCORRHEAL GROUP:

Case 1. E. C.; male; 42; locomotive engineer.

(1) Clinical Picture: (a) epigastric burning pain 1 to 1½ hours P.C. of 4 years intermittent duration, increased by food and alkalis (soda, etc.); (b) chronic sinusitis; (c) tender in epigastrium to palpation.

(2) Gastroscopies: 1/29/36 — Considerable mucus throughout stomach of gray tenacious and frothy varieties with slight congestion. Impression: Mucorrheal (superficial) Gastritis.

3/4/37 — Only scanty mucus present of frothy type, no congestion or other abnormalities.

(3) Treatment: Weekly nose and throat treatments for posterior ethmoidal sinusitis from 1/31/36 to 3/2/37. Adjuvant therapy, bland diet, antispasmodics, sedatives.

(4) Course: 3/2/37—Complete disappearance of symptoms for first time in four years—remaining asymptomatic until the present.

Case 2. H. B.; male; 54; unemployed.

(1) Clinical Picture: (a) anorexia, nervousness, constipation, upper abdominal "soreness"; physically, epigastrium tender to deep palpation.

(2) Gastrosopies: 3/1/35—Increased mucus in patches throughout stomach, grayish and whitish, tenacious in nature. Impression: Marked catarrhal gastritis.

1/13/37—Several atrophic segmented areas; one erosion of hemorrhagic nature; mucus +2.

2/24/38—Unchanged from last examination except no erosions, but rugal crests are reddened in congestive aspects. Impression: Atrophic Gastritis with former erosive and present congestive features.

(3) Treatment: Bland diet, emphasizing small, frequent feedings, alkali powders one hour P.C., sedatives, kaolin in alumina gel one hour A.C., antispasmodics.

(4) Course: Symptoms continue unaltered.

Case 3. A. T.; male; 24; tailor.

(1) Clinical Picture: (a) "indigestion" 3 years constant duration, (epigastric distress immediately P.C. with belching); (b) bloating sensation; (c) nervousness; (d) weakness; (e) physical examination negative.

(2) Gastrosopies: 1/17/37—Moderate superficial gastritis, with thick mucus patches and slight edematous features.

1/21/38—slight decrease only in mucus.

4/22/38—Considerably less mucus (+1); no edema; considerably improved.

(3) Treatment: 1/17/37 to 1/21/38—Bland diet, with small frequent feedings; colloidal kaolin in alumina gel, agar-agar, vitamin concentrates (Wheat germ), alkali powders P.C.; belladonna A.C.: 2% hydrogen peroxide lavages twice weekly for months.

(4) Course: Unaltered from 1/17/37 to 1/21/38. On the institution of hydrogen peroxide lavages, after two months, gained 6 lbs. (4/22/38), stronger, slight "indigestion," less nervous, feels much better.

DISCUSSION

These three cases are selected rather than a large series because each brings out the salient features concerning this form of chronic gastritis. Case No. 1 demonstrates the fact that many of these mucorreal, catarrhal or superficial gastritis patients will show satisfactory response when mechanical or focal infective agents are treated successfully. In this instance the treatment of diseased sinuses with purulent discharge into the stomach was considered responsible for the patient's "cure." Case No. 2 demonstrates the fact that certain of these superficial or mucorreal cases are going through an evolutionary development, this patient developing into the atrophic type and proving refractory to our accepted forms of treatment. This is the type described as the "Alternative" form by the French authors, having changed from one type to the end form, the atrophic variety. The significance of these changes remains unknown, but it is possible that continued observation will shed light on this subject. Particularly important is the fact that despite rigorous medical treatment his symptoms continue unabated. It should be recalled here that a great many gastric cancers have gastric symptoms for many years before the development of their carcinoma. Case No. 3 illustrates the fact that patients cannot be always treated by rote. He failed to respond to the usual methods of therapy for one year, including bland diet, with small frequent feedings, alkalis, sedatives, antispasmodics, commercial kaolin and other preparations, vitamins, etc. etc. However, upon the institution of a two months' course of hydrogen peroxide lavages, the patient promptly responded satisfactorily both as to the gastrosopy and clinical pictures. Hydrogen peroxide lavages (2%) have a place in our therapeutic armamentarium in selected cases. Whether they can restore a histamine achlorhydria to normal acidity remains a very dubious question.

ULCERATIVE, EROSION OR EDEMATOUS FORMS:

Case 4. J. W.; male; 23; counterman.

(1) Clinical Picture: (a) epigastric boring pain shortly P.C., relieved by food or alkalis of several months duration; (b) melena (twice); (c) anemia; (d) physical examination reveals oral sepsis (carious teeth, pyorrhea).

(2) Gastrosopies: 3/3/36—Numerous erosions and oozing with evidence of recent submucosal hemorrhages. Along the greater curvature just underneath the esophageal entrance a large U shaped ulceration which oozed freshly. A deep linear excavation lateral to this area. Impression: Erosive, ulcerative gastritis.

3/16/37—A few superficial pigmented spots present only. No ulcerations seen.

(3) X-ray—Gastro-intestinal series negative for pathology.

(4) Treatment: Strict, modified ulcer diet; alkali powders; antispasmodics; sedatives; high vitamin; dental care.

(5) Course: Completely asymptomatic from 3/10/36 on to date of last gastrosopy 3/16/37.

Case 5. C. W.; female; 49.

(1) Clinical Picture: (a) severe intermittent gripping pains in the epigastrium, P.C., relieved by food or soda—of 2 years intermittent duration; considerable nervousness; physical examination negative.

(2) Gastrosopies: 4/5/35—Several small circular erosions on the anterior wall, lesser curvature of the body. Fresh oozing from some. Impression: Erosive gastritis.

4/15/36—No erosions, only several dark brown pigmented spots.

(3) Treatment: Ulcer management, with modified Sippy, antispasmodics; alkalis; rest; sedatives; vitamins.

(4) Course: Gaining weight, occasional gassy distress on minor dietary indiscretion; greatly improved.

Case 6. W. M.; male; 53; machinist.

(1) Clinical Picture: (a) dull gassy distress with pain in epigastrium and left lower chest (over the heart) of 10 years duration; (b) dyspnea, palpitation and vertigo; (c) loss of 12 lbs. weight in past year; (d) physical examination negative.

(2) Gastrosopies: 1/14/38—Moderate edema, considerable tenacious mucus; several moderately large, dark erosions, also pigmented patches along lesser curvature pars media. Impression: Edematous, erosive and mucorreal gastritis.

2/1/38—Slight edema, slight tenacious mucus. No erosions, occasional pigmented spot.

3/4/38—Slight edema and mucus. No erosion or pigmentation.

4/5/38—Stomach almost within normal limits except for a very slight edema in the area of the incisura angularis.

(3) Treatment: Bed rest, ulcer diet (at first Sippy, later Modified); alkali powders; sedatives and antispasmodics.

(4) Course: On 2/1/38 after bed-rest, patient is considerably improved and all symptoms markedly alleviated. On 3/4/38 patient has gained 14 lbs., is completely asymptomatic and states that he "never felt better in his life." On 4/5/38 patient continuing to gain and felt in perfect health.

DISCUSSION

Case No. 4 demonstrates (a) that not infrequently gastric ulceration is picked up when expert roentgen-ray studies are negative. This is particularly true when the ulceration is not deep or is in the more proximal parts of the stomach; (b) Oral sepsis when marked, as in this patient, can be instrumental in production of a sub-acute ulcerative, erosive gastritis which can show prompt therapeutic response when the cause is removed and intensive treatment instituted. This patient was of the sub-acute variety, judging from the short duration of symptoms, the marked gastric changes and prompt response to treat-

ment. (c) When these cases continue for any length of time without rigorous treatment, it is probable that they go on to a severe refractory form as in Case No. 13 or as those cases where the European surgeons perform subtotal gastrectomy. Schindler has used the Coutard X-ray therapy in intractable cases, but because of the tremendous radiation involved we have not attempted this method. Case No. 5 shows that since mild symptoms and some pigmented spots were still present at the end of one year, that some permanent changes in the stomach had occurred, that therapy should be continued, and that a relapse could be experienced quite readily in all probability. Continued observation is therefore particularly indicated in this type of case. The question of Vitamin C deficiency in these erosive types is an important one since these patients frequently relate unbalanced dietaries, poor in vitamin content. This has particular reference to those clinic patients on the "welfare relief." Case No. 6 is especially interesting because of the symptoms referable to the cardio-vascular system, such as pre-cordial pain, palpitation, dyspnea, and vertigo. These were apparently due to gassy distention in the gastro-intestinal tract with reflex disturbances in the heart, as we have been able to demonstrate experimentally in the human subject. If these disturbances and reflex manifestations are permitted to continue over for prolonged periods, they can most certainly produce heart damage or cause sudden, dangerous and even fatal cardiac abnormalities, as we have shown. Other interesting features are the fact that the etiology in this case is unknown and yet the therapeutic response was remarkably prompt. One would have thought that because of the 10 year intermittent duration of symptoms an advanced and difficult gastritis would be present, and yet this proved not to be the case.

ATROPHIC GASTRITIS WITH HEMORRHAGIC, OR "MIXED" FEATURES:

Case 7. V. M.; male; 22; hosiery worker.

(1) Clinical Picture: (a) constant epigastric discomfort and pain about $\frac{1}{2}$ hour P.C. unrelieved by food or alkalies—1 year duration; (b) headaches (sinus disease) and post-nasal discharge; (c) nervousness; (d) weakness; (e) physical examination reveals tenderness particularly in the epigastrium, but distributed over the upper abdomen as well.

(2) Gastrosopies: 1/27/37 — Markedly segmented atrophic areas in the fundus, which were small in size. Diffuse arborization of the submucosal vessels in the fundus, also along the greater and lesser curvature, which were glazed. Rugae throughout definitely effaced. 3-4 smooth, punctate, reddish spots of a hemorrhagic nature in the fundus, with oozing; mucus +1 tenacious. Impression: Atrophic gastritis with erosive features.

2, 10/37 — Less oozing and hemorrhagic spots; slight congestion in fundus. Atrophic areas unaltered, mucus same.

3/1/38 — No hemorrhagic or oozing features. Atrophy still same. This tenacious mucus still present, but definitely lessened.

(3) X-ray findings: G. I. series negative. Marked sinus disease (antral and frontal). Gastric analysis: normal acidity.

(4) Treatment: Antacid powders, sedatives, antispasmodics; bland diet; vitamins; tonics;—finally submucous resection and nose and throat treatments.

(5) Course: Above medical therapy gave only slight improvement with symptoms unchanging until submucous resection and nose and throat treatments given intensively. Then for the first time definite improvement in the symptoms and gastroscopic picture noted.

Case 8. W. M.; male; 25; stone-mason helper.

(1) Clinical Picture: (a) frequent gassy distention and distress in the upper abdomen; (b) weakness and nervousness; (c) physical examination negative; (d) gastric analysis — normal acidity.

(2) Gastrosopies: 4/11/35—Mucosa quite atrophic in segmented areas, with arborization of many bluish vessels. Very glistening aspect of fundus. Impression: Atrophic gastritis Grade 2.

12/2/36 — Grayish mucosa, atrophic, patchy, venous arborization. One pigmented spot in fundus.

12/16/37 — Pale segmented atrophic areas in fundus and lesser curvature, anterior portion. Effacement of folds here. On posterior portion mid-fundus, oozing area from friable mucosa. Impression: Atrophic gastritis with friable mucosa.

(3) Treatment: Bland diet, small frequent feedings; rest; antispasmodics; sedatives; high vitamins; colloidal kaolin in alumina gel.

(4) Course: Moderate improvement; less nervous; less weak and gassy, but mild symptoms still present and exacerbated on working hard, mental strain, or dietary indiscretions.

Case 9. L. C.; male; 40; laborer.

(1) Clinical Picture: (a) intermittent epigastric pain and distress unrelated to meals; (b) pyrosis; (c) weakness; (d) physical examination negative; (e) acidity subnormal.

(2) Gastrosopies: 9/2/36 — Mixed congestive, atrophic (segmented areas with arborization) and mucorrheal (+2) gastritis.

10/23/36 — Moderate improvement, less congestion, less mucus.

3/11/38 — Still atrophic features, no congestion, slight mucus.

(3) Treatment: Bland "smooth" diet; alkali powders; antispasmodics; sedatives; vitamin concentrates.

(4) Course: Marked improvement, only slight symptoms present occasionally.

Case 10. S. G.; male; 55; machinist.

(1) Clinical Picture: (a) epigastric pressure distress several hours P.C.; (b) loss of 20 lbs. and weakness; (c) occasional tarry stools; (d) physical examination—epigastric tenderness; (e) hypochromic anemia (hgb. 60%); (f) histamine achlorhydria.

(2) Gastrosopies: 10/9/35—Moderate pallor in patchy areas—fundus and pars media with venous arborizations and moderate rugal effacement and friability. Impression: Atrophic Gastritis—Grade 2.

6/10/36—Color definitely less pale with less conspicuous arborizations, still friable.

1/13/37 — Friability to slight extent, but color within normal limits.

(3) Treatment: Feosol, dilute hydrochloric acid; hydrogen peroxide lavages; smooth bland diet; sedatives.

(4) Course: 1/13/37 — Blood count returned to normal limits; gaining weight; only occasional distress.

DISCUSSION

Case No. 7 demonstrates the importance of focal infective and mechanical irritant factors as with this marked sinus disease accompanied by heavy, purulent discharge. This is in all probability the advanced stage of Case No. 1, where a mucorrheal gastritis of sinusitis etiology occurred. However in case No. 7 the superficial or catarrhal form had probably progressed to the atrophic variety as in Case No. 2. This patient responded only slightly to medical therapy, but when submucous resection with amelioration of the sinusitis took place, a definite improvement in the gastroscopic and clinical picture occurred. Case No. 8 shows that certain of the atrophic varieties really are never free of symptoms, although with constant care, the patient may temporarily be free of symptoms. These cases are frequently those with easily upset, "delicate" or sensitive stomach where slight dietary indiscretions or strain, etc., will bring on symptoms. Case No. 9 illustrates that numerous cases with "mixed" features of atrophic, congestive and mucorrheal varieties in different areas in the same stomach, can improve

symptomatically when the associated congestion and mucorrhea respond to therapy and disappear from the gastroscopic picture. Case No. 10 demonstrates the fact that whereas the non-anemic types of atrophic gastritis remain unaltered under therapy, the forms accompanied by secondary or primary anemia will return to a normal gastroscopic picture under specific therapy with liver, or iron as in this case. The melena suggests hemorrhages from gastric erosions. Cases No. 7 and 8 show that normal acidities occur in the atrophic forms of gastritis, where the atrophic aspects are not diffuse. However, when a histamine achlorhydria occurs as in case No. 10, despite return to normal appearance, the achlorhydria remains, in our experience.

HYPERTROPHIC, MIXED FORMS:

Case 11. E. F.; male; 42; unemployed.

(1) Clinical Picture: (a) epigastric burning and hunger pains 2-3 hours P.C. intermittently for several years, relieved by food or alkalis; (b) considerable mid-epigastric pain to palpation; (c) normal acidity.

(2) Gastroscopies: 12/17/36—Moderate hypertrophic features fundus, anterior and posterior aspects. Antrum considerably congested and contracted. Moderate mucus throughout. Impression: Hypertrophic gastritis with congestive and mucoid features.

3/15/38—Antrum normal in color, no contractures. Hypertrophic fundal features still present. Slight to moderate mucus.

(3) Treatment: Strict ulcer regime with modified Sippy, rest in bed; alkali powders; sedatives; antispasmodics; vitamin concentrates.

(4) Course: Marked improvement clinically, only slight and occasional symptoms.

Case 12. M. T.; female; housewife.

(1) Clinical Picture: (a) mid epigastric discomfort and dull pains in the upper abdomen with nausea, of 2 years duration intermittently; (b) constant gassy distress and belching; (c) nervousness, sensation of lump in throat; (d) burning sensation in tongue; (e) physical examination—tenderness upper abdomen to palpation; (f) normal acidity.

(2) Gastroscopies: 5/9/35—Erosions in small area, excessive mucus, hypertrophic rugae. Impression: Hypertrophic gastritis, with erosive and catarrhal features.

4/3/38—Moderate pallor, effacement of rugae, arborization of veins in submucosa, oozing erosion. Impression: Atrophic gastritis Grade 2 with erosive features.

(3) Treatment: Smooth bland diet; alkali powders; carminatives; charcoal; colloidal kaolin in alumina gel; sedatives; vitamins; rest and bromides.

(4) Course: Continued exacerbations and remissions in symptoms every two months, upon any slight dietary indiscretion, emotional upset, or upper respiratory infection. Last gastroscopy done during exacerbation.

Case 13. I. C.; male; 23; movie manager.

(1) Clinical Picture: (a) sharp epigastric pain with burning sensation 30-60 minutes P.C. relieved by milk, cream or alkalis—5 months intermittent duration; (b) melena on two occasions accompanied by severe abdominal pain and vertigo; (c) marked nervousness; (d) physical examination—exquisite tenderness over epigastrium; (e) Grade 2 hyperacidity; (f) X-ray studies negative except for "spastic colon and adhesions."

(2) Gastroscopies: 4/30/37—Antrum spastic, contracted, hypertrophic, edematous with thickened angularis folds. Very marked granular aspect on lesser curvature. Impression: Mixed hypertrophic gastritis with edematous and spastic features.

4/5/38—Considerable spasticity throughout, angularis contracted and twisted, increased mucus, hypertrophic appearance and edema still present and mammelonated aspect on posterior wall, lesser curvature.

(3) Treatment: Following laparotomy 5/1/37 for suspected peptic ulcer, which was not found, strict ulcer

regime instituted, including 3 weeks bed-rest; alkali powders; continuous alumina gel drip; colloidal kaolin; sedatives; antispasmodics; modified Sippy; all ineffective, symptoms unaltered.

(4) Course: Following 8 months intensive therapy, sub-total gastrectomy performed. Upon greater lapse of time, clinical evaluation will be made.

DISCUSSION

Case No. 11 demonstrates the fact, observed in other cases, that hypertrophic mixed varieties can mimic the ulcer syndrome, particularly if the antrum is involved in the process. The marked improvement in symptoms was accompanied by the disappearance of the associated congested, inflammatory appearance of the mucosa, and lessening in mucus. However, exacerbations in these patients, where the gastric mucosa is persistently abnormal, are promptly produced by indiscretions, upper respiratory tract infections, stress and strain, etc. Case No. 12 shows that the hypertrophic form can develop into the atrophic form, despite our present therapy. Associated erosive features may persist. This patient appeared to have symptoms in cycles of 2-3 months, with remissions of equal periods. Exacerbations were usually precipitated by dietary indiscretions. This case as well as others in the hypertrophic variety point out the inadequacy of our therapeutic approach which is due to our ignorance of the actual processes which are operative in these transitions. If Hurst is correct in believing that the patients with hyperacid and anacid stomachs inherit this constitutional diathesis, it may be that hereditary factors in the hypertrophic and atrophic form of gastritis are similarly responsible. Case No. 13 points out (a) the fact that the "mixed" hypertrophic, edematous forms can simulate ulcer, when this is proven absent by roentgen studies and internal as well as external inspection and palpation of the stomach and duodenum during laparotomy; (b) that melena may be associated; (c) that despite the most intensive medical management and treatment as of ulcer, with 3 weeks bed-rest, etc. etc., a certain number of these cases have to be resected via sub-total gastrectomy, just as the medically intractable ulcer case. This is analogous to those severe gastritis cases where the European surgeons perform sub-total gastrectomy as a routine, often without preliminary medical trial. This recalls similarly some surgeons who did posterior-gastro-entrectomy or ulcer excision some decades ago for ulcer without recourse to preliminary medical trial.

POST-OPERATIVE GASTRITIS:

Case 14. S. P.; male; 65; former peddler.

(1) Clinical Picture: (a) sub-total gastrectomy for Gastric Carcinoma, proven pathologically, on 8/24/31, with a history mimicking gall stone colic of two years previous duration, no extension or metastasis; (b) within three months post-operatively had gained 13 lbs. in weight, felt stronger but from then up to 4/19/35 has had vague but considerable epigastric gassy distress and belching; (c) anorexia; (d) blood studies throughout have been entirely normal up to the present time; (e) histamine achlorhydria present throughout; (f) vague upper abdominal tenderness to palpation.

(2) Gastroscopies: 4/19/35—Marked congestion throughout, particularly on the rugal crests. Increased mucus. Projecting knob of tissue seen on the lesser curvature, probably the result of a cicatricial contraction following gastrectomy.

5/24/35—Appearance unaltered.

10/30/35—Appearance unaltered.

2/21/36—Appearance unaltered.

4/19/38—mucosa still reddened and congested. The rounded knob of tissue previously described still unchanged, on the lesser curvature. Friability of the mucosa with slight oozing on the posterior wall. Large amount of

thick tenacious mucus. Impression: Post-operative gastritis with congestive, friable, and mucorrhea features.

(3) Treatment: For the first four post-operative years dilute hydrochloric acid, small frequent feedings; rest; tonics; enzyme mixtures. No medication or dietary past 3½ years.

(4) Course: For the first four years, post-operatively, vague considerable epigastric gassy distress and belching, with rare upper right quadrant colicky pain, radiating to the right shoulder. During the past 3½ years the patient was practically symptom-free and abandoned medication and diet, "eating everything." Weight constant but at times feels weak.

Case 15. T. B.; male; 36; brakeman.

(1) Clinical Picture: (a) mid-epigastric hunger pain 1½ to 2 hours P.C., immediately relieved by food or alkalis, intermittently for 3 years duration—one year previous to emergency pyloroplasty for ruptured pyloric ulcer and 2 years after despite ulcer regime; (b) one year after pyloroplasty, cholecystectomy done for gall stones, and search made for peptic ulcer on operating table, none found in stomach or duodenum; symptoms still persist; (c) physical examination—considerable tenderness over the epigastric area; (d) gastric analysis—Grade 1 hyperacidity.

(2) Gastrosopies: 1/21/36—Marked hypertrophy of the rugae noted in the lower fundus. Moderate congestion and increased mucus throughout. Intensive spasm and contracture of the angularis. Impression: Hypertrophic gastritis with congestive and spastic features.

12/23/36—Less congestion and mucus; decreased spasm, hypertrophic features constant and marked.

2/22/38—Hypertrophic and other features unchanged.

(3) Treatment: Strict ulcer regime, Modified Sippy; alkali powders; colloidal kaolin in alumina gel; pure alumina gel; antispasmodics; sedatives.

(4) Course: After pyloroplasty, slight relief on ulcer regime; but symptoms moderate and persistent throughout, and unaltered by removal of gall stones. Referred for roentgen-irradiation.

DISCUSSION

Case No. 15 as well as some others in our unpublished series demonstrate that a hypertrophic form of gastritis can continue to produce the ulcer type of pain. This is in keeping with the Scandinavian school under the aegis and stimulation of Knud Faber. For example Andersen (27), Dahl, Holsti, Nicholysen and others have operated upon cases diagnosed as chronic ulcer, only to find gastritis and duodenitis which in their experience could produce duodenal deformity or spasm. This patient similarly demonstrates the fact that the gastric post-operative case is left with a gastritis which may or may not be symptomatic, and which does not appear to respond to treatment. The disturbance in the circulation and nerve supply created by surgery on the stomach may be the contributing factors. This patient has experienced slight relief following both operations, but his hunger pains 1 to 2 hours after meals still persist despite the intensive therapy. Several other intractable patients including this one with the hypertrophic variety are now being treated by deep roentgen therapy, using 15 weekly treatments of 50 Roentgens each. However it is too early to judge results as yet. Case No. 14 is of great interest because of the duration of recovery, being asymptomatic 7½ years after removal of a large carcinomatous mass saddling the lesser curvature, the malignancy measuring 10 x 4 cms. Symptoms were of two years duration pre-operatively. It is also noteworthy that in the absence of any therapy, the blood picture is entirely normal and the patient asymptomatic, despite the age (65 years). Just as in other cases it is noted that the inflammatory reaction may be temporarily asymptomatic, so peptic ulcer in some individuals may be unaccompanied by symptoms and not even suspected until ushered in by a sudden hemorrhage. Of a similar nature are the peptic

ulcer cases with brain tumor, as Cushing has shown, in which no gastro-intestinal symptoms are present. In the same category are the observations of certain pathologists as Robertson (28) at the Mayos, who found in 1926 that as much as 12% of routine autopsied cases, when carefully studied show evidence of old peptic ulcer scar, etc. Although some of these patients have had gastric complaints, many have not.

SUMMARY

1. Our present methods in the treatment of chronic gastritis are outlined and discussed.

2. Present therapy objectively, and sometimes subjectively, in the hypertrophic and non-anemic forms is inadequate, due chiefly to insufficient knowledge of pathological processes.

3. The congestive, edematous, catarrhal, ulcerative and erosive forms of gastritis are usually most responsive to medical therapy as viewed objectively and subjectively; i.e. by gastroscopic observation and clinical evaluation of the patient.

4. New therapeutic approaches in chronic gastritis should be investigated, particularly with reference to (a) hypertrophic, verrucose or mammelonated forms and (b) non-anemic atrophic forms.

5. The gastritis problem should be studied jointly and interdependently by the pathologist and gastroscopist clinician for the purpose of achieving a better understanding of the nature of gastric changes in health and disease. Such studies may also reveal the pathogenesis of gastric ulcer and carcinoma.

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DISCUSSION

DR. EDWARD B. BENEDICT (Boston, Mass.): Mr. President and Members of the Society: I have enjoyed Dr. Swalm's paper very much. I should like to comment on the classification first. It seems to me that until we have performed more gastroscopies, we should still adhere to Dr. Schindler's classification very strictly, as he has had so much more experience than anyone else in this country.

When we speak of congestive, hemorrhagic, erosive, ulcerative, or edematous gastritis, I think we are only confusing the picture. We can speak of superficial gastritis with edematous features, congestive or hemorrhagic features, and we can speak of hypertrophic gastritis with these features, and atrophic gastritis with these features, but it is important, I feel, and quite possible clinically to stick strictly to Schindler's classification so that in the literature there will be no confusion.

When Dr. Swalm states that hypertrophic forms do not respond to therapy, that they are refractory to all treatment, I think he must be referring solely to the gastroscopic picture, because certainly clinically many of these patients are cured for long periods of time.

With regard to the treatment of gastritis in general, I think Dr. Swalm has covered almost all the features, but I should like to emphasize particularly the importance of the teeth in gastritis; as a matter of fact, I think that dentistry should be more closely connected with gastroenterology and medicine in general than it is at the present time, and I think, particularly in gastritis, the teeth are of paramount importance.

I also feel that alcohol, tobacco, general hygiene, and diet are important. Dilute hydrochloric acid has been found very effective in the atrophic types with anacidity, and in some of the hypertrophic types with anacidity. The administration of alkalis is also important.

With regard to gastric lavage, most of our patients have responded without the necessity of lavage, and we have not had occasion to have much experience with that method.

Bed rest has also been largely unnecessary in most of our cases except in the very acute and hemorrhagic varieties where I think bed rest is important.

With regard to surgery, I think that should be almost wholly confined to the cases which have had hemorrhage. Thank you!

DR. ERNEST H. GAITHER (Baltimore, Md.): I do believe that gastritis is a proven disease entity. It is my wish not to be known as a reactionary or a pessimist, and my desire at all times is to align myself with the progressives; however, I do consider that the diagnosis of intragastric lesions is not quite so simple a problem as one might be led to believe after reading some of the reports presented during the past few years.

As to the diagnosis of gastritis, it is, in my opinion, not so easy and simple as it might seem, and what one observer would consider truly indicative of this condition would not be so diagnosed by another equally skillful observer.

The mucous membranes of the body in the conjunctiva, nose, mouth, throat, rectum and bowel, differ greatly in

every individual, as do the facial features and conformity of bodies; however, just because there is a difference, one is not justified in arriving at the conclusion that disease is present.

We must remember that while the present instrument is one of splendid accomplishment, yet it has by no means been perfected and we cannot obtain a very satisfactory picture of the proximal (silent) area. Again, it is certainly no easy task to visualize and adequately describe a duodenal ulcer, and it is in this area that the majority of peptic ulcers occur; furthermore, it is most difficult to differentiate between benign ulcers and those undergoing early malignant changes.

Certain it is that in the majority of gastrojejunal ulcerations, the lesion cannot be visualized.

Much progress has been made in this most valuable diagnostic adjunct; however, much more is to be accomplished, and we shall note continued progress; however, my plea is that we continue our intensive studies, encouraging the technicians to further efforts looking toward an improved instrument, and advising all clinicians to continue their intensive studies in the presence of a sane and judicial attitude, well remembering the limitations of the method, and not allowing our enthusiasm for its value to outweigh our good judgment.

DR. RUDOLF SCHINDLER (Chicago, Ill.): I enjoyed Dr. Swalm's and Dr. Morrison's paper very much and I am very happy that they have confirmed many of my previous opinions, especially about the difficulty of curing hypertrophic gastritis. I think if one tries to evaluate a therapy for a disease of such a long duration, as chronic gastritis is, one can come to definite opinions only after a very long period of observation.

It is necessary at first, and perhaps this could be answered to Dr. Gaither, to have a very good knowledge of the normal gastric mucosa. If one has an opportunity, which is so difficult in this country, to get a knowledge of the mucous membrane of the stomach of many entirely healthy people, one will find there is such a thing as a definite picture of a chronic gastritis, and then only it becomes possible to follow the course of such a disease as chronic gastritis through long years. Naturally, it is not very good to combine too many different kinds of therapy, because one will not know which was successful and which was not.

There are many cases of superficial gastritis and also of atrophic gastritis, which improve definitely without any therapy, and it is extremely difficult to say that a certain therapy was valuable. I had the opportunity, however, to follow one case of ulcerative gastritis over a period of ten years without seeing any improvement of the clinical condition or the gastroscopic picture. When this patient was treated with high voltage X-ray therapy after Coutard, all the symptoms and manifestations disappeared completely. In this one case we can say that therapy was effective. And after similar observations I would like to emphasize that I think superficial chronic gastritis is less prone to develop into the atrophic or dangerous form when frequent lavage is used, and I think this is valuable therapy. Silver therapy is less recommendable because some patients show increased irritability and increased pain.

I have seen one case of atrophic gastritis without pernicious anemia which responded to liver therapy confirming the observation made by P. Chevallier.

I entirely agree with Dr. Benedict in the points he brought up.

DR. CHESTER M. JONES (Boston, Mass.): I think it is obvious from Dr. Swalm's paper, which brings up many interesting points, and from the discussion to date, that the Association is due for a good many papers on gastroscopy for many years to come. We may be about to run the gamut on gastroscopy that we have already run in the discussion of peptic ulcer.

After reading Dr. Swalm's paper, and after reading Dr. Schindler's book on gastroscopy, I feel certain that we still do not know all of the variations of the normal stomach. I am sure there are going to be a large number of cases, without symptoms, labeled gastritis because of what was seen on gastroscopy. I think one cannot lay too much emphasis on the necessity for knowing all the variations that may occur and still be within normal limits. For example, what are the variations in the appearance of the normal stomach in the different decades? I am sure that one will get different gastroscopic pictures at different periods during life, and one could easily make the mistake of saying "This is gastritis," when, as a matter of fact, the changes were merely those normally incident to the fifth or sixth decade.

There is one point mentioned by Dr. Swalm which I think warrants a little comment. He has referred to the gastric changes noted in pernicious anemia as being those of atrophic gastritis. My own impression, from following some of these cases with Dr. Benedict, is that the term atrophic gastritis is a misnomer when applied to pernicious anemia, and I think this may possibly be true of other deficiency conditions. Dr. Swalm also referred to the non-anemia anemias, an expression which, I think, indicates that in his mind, as well as in mine, there is a real doubt as to what the situation implies. I am sure that there are degenerative gastric changes caused by deficiency conditions which mimic atrophic gastritis closely and which are very hard to distinguish from pernicious anemia. These changes are entirely comparable to the atrophy noted in the tongue and the rectal mucous membrane, and yet under proper liver therapy there is a striking return toward a normal appearance. A similar condition, I think, undoubtedly holds in pellagra, and Dr. Ruffin and Dr. Borland have both told me of recent observations they have made of pellagra patients. Their observations would seem to bear out this suggestion—that the atrophy in deficiency conditions is not that of gastritis. It is important that all such variables be thoroughly studied and understood as they occur in normal individuals and in patients suffering from nutritional disorders.

DR. WALTER L. PALMER (Chicago, Ill.): Mr. Chairman, the other discussants have said about all that I wanted to say, but I will reinforce their remarks by a few more or less categorical statements.

I do not wish to be considered a heretic or a reactionary any more than Dr. Gaither does, but the situation calls for a few frank statements. I am convinced that anatomically there is such a thing as gastritis. I am quite convinced that there are symptoms resulting from hypertrophic gastritis and postoperative gastritis. I am not at all convinced that there are any symptoms from atrophic gastritis or superficial gastritis.

We know nothing about the etiology of any type of gastritis. We know very little about the course of gastritis. Our experience has certainly shown that gastric changes may occur rapidly in the gastric mucosa. One gastroscopic examination may show a normal appearance, another, a superficial gastritis, another, an atrophic gastritis, and another, a hypertrophic gastritis. If such changes can occur in a few months' time, what does it all mean?

I question very much the wisdom of studying the effect of treatment on gastritis until we know more about the nature of the condition or disease, whichever it may be, its cause, and its natural history.

The list of the various possible causes supports this point of view: foci of infection, alcohol, faulty hygiene, reflex disturbances, contiguous pathology, regurgitation, autonomic nerve imbalance, etc. The multiplicity of treatments likewise illustrates our lack of definite knowledge: hydrochloric acid, vitamins, drugs of all kinds, gastric lavage, and so forth. I suspect that the same therapeutic results could have been obtained by psychotherapy, pure and simple.

DR. DAVID H. ROSENBERG (Chicago, Ill.): I have had the privilege of treating two cases of combined superficial and atrophic gastritis and one case of hypertrophic gastritis, diagnoses of which were made by Dr. Schindler from gastroscopic examinations, by means of parenteral liver extract, and in none of these cases have we noted any improvement gastroscopically. One case of atrophic gastritis, in fact, showed a progression of the mucosal lesion. In the case of hypertrophic gastritis we did not anticipate any improvement by such therapy.

It would seem that what Dr. Jones has suggested may be true; that when we are dealing with true gastritis, liver therapy may not produce the same dramatic results which he, as well as others, have observed in the treatment of so-called atrophic gastritis associated with pernicious anemia, and that the latter form of gastritis may be really a deficiency disease or its manifestation.

DR. ELMER B. FREEMAN (Baltimore, Md.): I would like to say a few words in reference to the classification of chronic gastritis and the gastroscopic appearance of the gastric mucosa in pernicious anemia. With our present knowledge of chronic gastritis, I feel very strongly that we should adhere to a very simple and concise classification. For clinical purposes, I know of none better at the present time than the one Dr. Schindler has given us and which also has been stressed by Dr. Benedict.

From gastroscopic studies, I do not believe that the changes in the gastric mucosa which occur in pernicious anemia are the same as those which occur in chronic atrophic gastritis. Certainly, the gastroscopic appearance is entirely different.

DR. WILLIAM A. SWALM (Philadelphia, Pa., closing the discussion): We are merely presenting the results of our observations for the past four or five years and I am very glad that we did so because it has brought out some very interesting discussions.

So far as classification is concerned, of course, Dr. Schindler surpasses us all in experience. We are associated with an artist, Dr. Jackson, one who believed that at least thirty different varieties of gastritis could be seen, even before Schindler's 'scope was invented. This caused us to hesitate to accept the classification into four varieties as we should think it should be. We really still believe that the classification will change in spite of all that has been said today.

We also agree that many of these cases do not need lavage. We did not lavage one-half of our cases.

Dr. Schindler says he thinks there are too many therapies. We gave you a compilation of all the therapies we could possibly get together, and we have tried them all out. After all, in America, the patient wants results and doesn't desire to be a guinea pig. Therefore, we employed total management.

Dr. Jones believes also the statement regarding the variables in symptoms. Symptomatically chronic gastritis is a difficult thing to diagnose and, of course, our observations are based on the gastroscopic findings, together with a careful examination and routine studies. Everyone who went through our clinic had "the works," just as Dr. Lyon does it, and you know how thorough he is.

I had always believed the same as Dr. Jones does, that pernicious anemia was not a gastritis with pernicious anemia, until I saw the slides of Knud Faber, where he showed the abnormal histologic changes and revealed that it is an inflammatory condition. Personally I did not think so either at that time, and it is interesting that Dr. Jones picks up the same former trend of thinking. It may be that these pernicious anemia cases of Knud Faber's were complicated cases and may have had pernicious anemia with secondary gastritis and not primary gastritis with pernicious anemia.

I am always interested in hearing Dr. Palmer, especially since he is linked with Dr. Schindler, and when he says that he is still somewhat doubtful about the nature, cause,

and so forth of gastritis, it almost makes one feel as though one should sit down. He has watched Dr. Sehindler, who instructed me, and still believes that the nature, cause, etc., are not established.

As I said, our work is a compilation of all authors, and

we attempted to treat our patients in a total management way, the same as most of you do. If you do not help your patient one way, you will often swing to another, even if you do have to resort to psychotherapy, which we think is an important factor as well, just as Dr. Palmer does.

Psychiatric Contributions to the Study of the Gastro-Intestinal System

By

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IN limiting myself in this paper, I have kept in mind three fields—the gastro-intestinal system, its connections with the rest of the patient through the endocrine and autonomic nervous systems, and the mental field, connected with the other two. I shall discuss this last field.

The psychiatrist finds opportunities to study the gastro-intestinal tract first in his psychotic patients. A few cases will illustrate the ways in which digestive symptoms are built into the psychoses, and used by patients.

A woman of 48, referred for involuntional melancholia, had never in childhood been without a digestive disturbance; she had always been sickly and pampered. Her conscience was always uncomfortable and drove her to become a missionary; all arrangements were completed when she was prevented from carrying them out by typhoid fever, of all diseases. After this she went back to her preoccupation with nausea and vomiting—her chief life occupation.

In cases of early dementia praecox in three boys aged 16, 18 and 20, descriptions are available of digestive events of early childhood. In all appeared neurotic oversolicitous parents. Vomiting, refusal of food, colitis began in infancy and continued as methods to dominate the family. One boy gets out of school by nine o'clock vomiting; another, "when his sick stomach does not allow him to work, spends his time fishing, gunning, or fox-hunting." In all three boys, delusions now cluster about these preferred gastro-intestinal reactions.

A story of feeding difficulties was obtained and verified in a girl of 13 with dementia praecox. The mother's main object in life was, and still is, to feed this child. But the child bit and scratched during early breast feeding; she refused milk from a bottle. Description of feeding difficulties are taken from hospital records when the child was two years of age. She grew up on a limited diet: she broke any milk bottle she could find; she refused to come to family meals—she ate by herself irregularly—she bit and scratched other children, and for this reason she was dismissed from school. At a hospital school she gained in ability to get on with people but she became emaciated, when she was not forced to eat. Her mother preferred the other side of the dilemma and placed her in a mental hospital where she was tube fed, gained thirty pounds, and became katatonic. She could not be well nourished and well behaved at the same time.

If we turn now to patients whom the psychiatrist would call "neurotic," we find many of them referred

by internist and pediatrician. And in these cases the use of the digestive symptom as a symbol stands out clearly.

A woman says: "I struggle between a feeling of being dirty and a reluctance to brush my teeth or go near a dentist. As an infant I nearly starved because I would not take milk. Now I am babyish—I can't talk."

A college girl as a baby had been coaxed to eat. At 8, when her curls were cut off, she had a severe diarrhea. In college she had to read cookbooks all day; she had to supervise the preparation of her own meals: she became emaciated.

Psychiatric contributions to the diagnosis and treatment of disturbed functions of the digestive tract center about four considerations. It is taken for granted that investigation of organic factors has first been made without yielding a full explanation of the condition and a clear line of therapy. After this search, what suggestions can be made to the general physician, the gastro-enterologist and the pediatrician?

(1) Fundamental is the need to manage infant feeding according to Aldrich's method for preventing anorexia (1) and Gesell's suggestions (2). Aldrich outlined a plan which included marked reduction in diet at the first sign of anorexia, avoidance of sudden changes in food and of close supervision by parents and pitched battles at meal times. Equal interest in the training of sphincters should be shown by the attending physician. Both of these constructive preventive measures are aimed at keeping the parents from showing anxiety disproportionate to the situation. If this infant training could be well done, symptoms as they come to the gastro-enterologist and psychiatrist would be greatly modified for the better.

(2) With conditioned autonomic reflexes in command of many gastro-intestinal disturbances, efforts can be made in reconditioning. When colitis or vomiting are results of known emotional stimuli, a complete change in the emotional state of the family may break the chain. For example, if vomiting is welcomed and expected instead of dreaded, it may stop. In colitis, if the stimulus is brought on with the bowel empty, it may lose its effect.

If early signs of emotional excitement appear, Cannon suggests that it is best not to eat until the emotional reverberations have died down.

(3) Psychological conflict, a rather vague term to the physician, was partly brought to book when the physiologist discovered the autonomic nervous system.

A child at dinner with a big appetite and a big sense

of guilt (or fear of a stern parent) has a conflict between the antagonistic cranial and mid-autonomic divisions for the control of the stomach.

Going further, some conflicts are so disagreeable, so shameful, that they are put out of consciousness. A craving is met by refusal to recognize it, which means a continued stirring up of the appropriate autonomic path. "Repressed affect," says Kempf, "seems to be stored (like a coiled spring) in the heightened postural tension of the autonomic apparatus."

One roentgenologist suggests watching the colon under the X-ray when searching for an emotional conflict. He says that the expression of the colon is more honest than that of the face.

Apparently there are emotional repressed factors even in ulcerative colitis. Sullivan and Chandler (3) report that symptoms of ulcer followed directly upon specific emotional disturbances. A personality study of the adult patients showed that all were immature. In these cases psychotherapy was used with good results.

(4) The foregoing considerations may have prepared you for the last step—into psychoanalysis. More specifically I want to give you suggestions derived chiefly from Freudian investigations. I find it hard to evaluate them.

No one would deny, I think, that any strong emotion has a general bodily resonance and will express itself in that organ which is the weakest link, which has been in some way conditioned, sensitized. Nor can there be much doubt as to certain organs being symbols—in common life, in child life, in the vulgate. The mouth symbolizes taking in, incorporating, loving—more than once I have heard delirious patients talking of devouring their mothers. The stomach symbolizes disgust, for one thing. Cardiospasm can come when an annoyance, an insult, has to be swallowed. Leaving out of consideration the small intestine, it has been harder for me to be sure of the symbolization of the colon. Certainly for children, and for many childish adults, the operation of the colon—rectum—sphincter is the most important event of a day. The psychoanalyst says this organ symbolizes giving; in infancy something given to the world to get a mother's praise.

After this introduction let me quote exactly the results of studies of colitis in the Chicago Institute for Psycho-analysis. "In all of these patients we find an increased inner urge to give to others, to make restitution, and to compensate for aggressive acquisitive wishes. This urge to give expresses itself in the form of increased elimination of intestinal content instead of giving of real values. This increased elimination also expressed an aggressive attack on others. It is a substitution both for a gift and for a hostile aggression." By the analysis of 5 patients with colitis, 4 have been freed of their symptoms without any special diet.

In the Chicago series another group included gastric neuroses and duodenal ulcers. In these patients was found the demanding attitude which was met either by an internal shame and guilt or was thwarted by external circumstances. "As the demand for love, service, and protection since early infancy is closely associated with the wish to be fed, the unsatisfied demanding conditions serve as a permanent stimulus of the stomach. They mobilize the wish to be fed which

becomes independent of the periodic organic hunger and leads to permanent irritation of the stomach—"chronic neurosis or ulcer."

Last week I heard about an ulcer patient from Dr. Draper, with his anthropological slant. Stomach pains began when his wife suddenly told him that she was pregnant. "His world dropped out from under him." Ulcer developed, and Dr. Draper says it was maintained by a milk diet. At the time of a later pregnancy the ulcer bled. The man had had several emotional upsets: he resented his wife's fondling the baby instead of himself: he felt that a "rival had taken his wife away": he felt like "killing the baby."

There are some guides to personality study which emerge from all these considerations.

In every functional and most organic cases psychiatrists would urge consideration of the patient's personality under these headings.

(1) Early eating habits and early attitudes toward family, school work, life. (2) Present day emotional stresses and strains, frustrations, happiness or unhappiness, especially in marriage. (3) Does the patient make his gastro-intestinal organs the symbol of anything?

Such study should be given at least one uninterrupted hour. It often happens that a patient will fill the first half hour with organic complaints, coming in the second half hour to emotional attitudes. Such patients say that they never have had a chance to tell their whole story until they came to a psychiatrist. This full hour is important, although I can agree with Dr. Crothers that in the stress of practice it is immensely difficult for an hour to be given without neglect of other duties. The listening doctor can take in statements in any order but should then arrange them chronologically. The patient's personality should emerge as an integrated system of habitual adjustments to the environment—especially to other people and to food.

There should then be no attempts to classify the patient. Description is better and safer. Psychiatrists are beginning to distrust most classifications of personality as inadequate. There are definite psychotic and neurotic patients. But they are small in number as compared to the great numbers of people who are simply unhappy, tense, frustrated or resentful. In all sorts and conditions of men there is need to watch for emotional conflicts displaced to the digestive tract.

With a description of personality tied up with the other symptoms, the whole situation of the patient, that is, the complete diagnosis, will be ready for use in treatment.

In closing, a sentence is appropriate from a paper given to this Society in 1932 by Dr. Adolf Meyer: "Often the gastro-intestinal tract with its receptive, digestive and eliminative functions can become that which expresses and leads the personality . . . throughout life."

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DISCUSSION

DR. FRANKLIN W. WHITE (Boston, Mass.): I am not a psychologist, and I am not sure that I am qualified to discuss a paper of this kind, but Dr. Bond has shown us how digestive symptoms are built into the psychoses, and I am sure in listening to him we realize that he sees

a certain group of patients who are perhaps more likely to go to the psychologist than to the man interested in digestive diseases.

He stressed the importance of psychiatric study. Every history is in some way a personality study. If a patient sits down and tells us his troubles, by the time he has talked for a half hour we have sized him up; we know something about his day, his habits, his hobbies, his joys and sorrows; he has given us more than a picture of his digestive symptoms; he has given us a picture of himself.

Of course, this takes time and, as Dr. Bond has said, when the patient comes to a stomach specialist, he tells about his stomach first, and only after a half hour or so does he begin to unburden himself of some of these secret and other troubles which are so important.

I think perhaps the commonest things, which we will simply mention, are the direct effects of emotion on the digestive tract, so well known to us all, the nervous vomiting, nervous diarrheas, and so forth.

Then Dr. Bond has spoken of something more deep-seated and elusive, these concealed or unconscious effects, which he has explained by the Freudian conception of a symbolism in the gastro-intestinal tract, that these various digestive symptoms are outward signs of repressed mental conflicts.

This whole situation brings us into real, practical mistakes and difficulties, without doubt. It is a very common mistake to exaggerate the discovery of some minor physical ill or something which turns up on physical examination. We find a local tenderness, or a little too much or too little acid, or a doubtful Graham test, or some malposition of the pelvic organs, and may overlook the powerful psychic factor which is the real cause of the symptoms.

Recently, I saw a patient who told me of her eighteen operations; it seemed as if everything in the abdominal cavity had been taken out or tinkered with, and only after about an hour's talk did I discover the major factor, a perfectly unbearable home life; while all these operations had helped very little or even made her worse, she responded at once when she was taken out of her home surroundings and given proper psychotherapy.

Another difficulty may sometimes appear in seeing psychotic patients in sanatoria. A middle-aged woman loses her appetite, and loses weight, and has local pain, and the question arises, is she developing a cancer in the abdomen? These symptoms require careful study but often enough in such cases are merely a manifestation of psychotic troubles.

I have made the simple observation a number of times in the psychoses, that the patient who comes in at the time of an active wave of depression has a lot of gastro-intestinal symptoms, and when that cyclic psychotic depression disappears, then the patient is entirely symptom free so far as the digestive organs are concerned, until another wave of depression appears.

As to ulcerative colitis, it perhaps has occurred to many of us to wonder whether the colitis eases which Dr. Bond was speaking of had simply an irritable colon or whether they really were patients with deep-seated organic change.

I should like just to say a word about some recent work done by Dr. Lium, a surgical resident at the Boston City Hospital, with reference to the etiology of ulcerative colitis. He has made colonic explants in a number of animals and watched them, and finds that when we have stimulating factors which cause spasm and irritation, the injection of some toxins, drugs which act on the parasympathetic system, etc.—we have first, spasm of the explant, followed, often enough, by irritation and ulceration. Since emotion surely causes spasm, there is a possibility that some of these cases of colitis may develop in this way.

With regard to treatment, I have one question. Of course, we all try to allay the fears of these patients, to

banish the thought of cancer or serious disease of any kind, and try to encourage them, and carry out proper hygiene, with rest, or gentle exercise, and the use of sedative drugs in a judicious way, and try to teach them some simple philosophy of life which will lessen their anger and excitement and rush and grief. I should like to ask Dr. Bond whether he feels it is within the scope of the ordinary internist to go a step further and try to unearth some of these unconscious emotional conflicts, which seem to be so very important, and to try to get rid of them.

I think we all ought to be grateful to Dr. Bond for discussing the psychic source of so many gastro-intestinal symptoms.

DR. ALBERT J. SULLIVAN (New Haven, Conn.): Dr. Bond has given us some exceedingly valuable material and he very kindly and gently hinted that it is up to us to put it into practice.

For some years I have been spending from one-half hour to an hour and a half on the study of personality factors in every patient who has come to me, irrespective of the diagnosis, that is, whether the condition seemed to be an organic disease or purely a functional one, and last week I reviewed two hundred cases on which I had the follow-up of at least eighteen months, and attempted to group them according to the importance of emotional factors.

That has been done numerous times in the past but usually with an "either or" classification, that is, the patient either had organic disease or had a functional complaint.

I found very shortly that my cases could fall definitely into four groups. The first class was a group of patients who had no organic disease of the gastro-intestinal tract, and the symptoms were entirely emotional, not organic. In this group was a large number of anxiety states, a few actual psychoses, a few which could best be described as Dr. Alvarez terms it, as "insanity equivalents." This group makes up 18 per cent of the total number of patients. In my estimation the treatment of this group is entirely psychiatric. Much of it can be done by the internist or the gastro-enterologist. Some of these patients may improve temporarily on a series of injections or hospitalization, or a therapy which removes them from their environment, if they go to some sanatorium or clinic, but they will promptly relapse and their symptoms recur, when they get back into the environment which is causing the difficulty.

The second group of patients consists of patients who have no organic disease. The symptoms are due to a combination of emotional factors and poor habits and malfunction. For example, there is the irritable colon and the mucous colitis patient. There is no doubt at all that habits of eating, enema habits, cathartic habits, play a large role in those cases, and there is no doubt in my mind that emotional factors play a large role. The treatment is a combination of psychotherapy, if that is what you wish to call it, and dietotherapy, and change in the patient's habits of irritating the colon by cathartics or enemas. That group makes up 25 per cent of the total group.

The third group is a group which most of you would probably feel is an artificial group, but it is a group which I feel very definitely about. It is a group of patients with definite organic disease but, in my opinion, in these cases emotion plays a very large role in the etiology, particularly in the onset of recurrences, and I speak chiefly of two organic diseases, most peptic ulcer cases, and most cases of ulcerative colitis. That group makes up 27 per cent of the total.

The fourth group is a group in which organic disease plays the whole role and emotional factors have little or no significance, and that group is made of such things as carcinoma, cholelithiasis, cirrhosis of the liver, and things of that sort. This group is 31 per cent of the group.

DR. RUDOLF SCHINDLER (Chicago, Ill.): In 1927, von Bergmann, of Berlin, published an important paper on the tearing down of the organ neuroses.* He contended that in many cases in which formerly we would have diagnosed them as neurosis, improved methods of examination, such as cholecystography, biliary drainage, gastroscopy, have taught us the presence of severe anatomic changes.

This certainly is true, but we should not forget the great role which psychic influence plays in organic disease, as Dr. Bond stated, so that in almost every instance of chronic disease, except operable carcinoma, the question arises whether systematic psychotherapy would not be preferable to somatic treatment. On this point I entirely agree with Dr. Palmer, although I believe that superficial and atrophic gastritis have very definite symptoms. Moreover, evidently genuine organ psychoneuroses exist and they develop especially in the alimentary tract, for reasons well known to the psychiatrist, and described by Dr. Bond, especially the symbolism of the organs, which is so obvious and cannot be overlooked.

What we need is a definite prognosis and indication for the special therapy in each case. Not every patient should be analyzed. Take for instance, the frequent, though usually not diagnosed, proctostasis, that form of obstipation in which the rectum has lost its sensitivity, the ampulla being filled with feces without the patient's feeling it. In my experience only a very few cases have simple causes such as bad habits at the act of defecation and respective conditioned reflexes. Most of them are genuine psychoneuroses. These again may be subdivided in two categories. One of them concerns young unmarried girls. The disturbance lies very superficially only, and can be treated by simple persuasion and simplest forms of suggestion. This type of therapy is useless in the second form. If patients of the second type are analyzed, severe infantile regression is found. These cases need thorough psychoanalysis. The "depth" of this psychoneurosis is great.

Most cases of cardiospasm are cases of genuine organ psychoneurosis, and surgeons, as Sauerbruch, have described how easily it may be cured by simple hypnosis. Its depth is not great. Such cure, however, is possible only in about the first half-year after the start of the disease. Later the reflex is conditioned, and psychotherapy becomes useless.

The reason for psychogenic diarrheas may lie extremely superficially, so much as not to need any therapy. In other cases these diarrheas are so deeply rooted in the personality of the bearer that extensive analysis is indispensable. What we need, therefore, is: to come to *correct indications* for psychotherapy by the use of all methods of examination and by the determination of the "depth" of the neurosis, and to suggest the *proper kind of psychotherapy*, which depends on this "depth," on the duration of the disease, on the age of the patient, and on other factors, such as surroundings, intelligence, and so forth.

DR. JOHN L. KANTOR (New York, N. Y.): I should like to say a few words from the point of view of the practising physician. It seems to me we would like aid from the psychotherapist, and we need it, but the cards are so stacked against him that I am not sure much can be accomplished. Unhappily, there seems to be a great deal of fatalism about this type of patient. In the first place, he is presumably endowed with an unstable psyche by virtue of inheritance; and, secondly, he seems to be tremendously buffeted about by the strain of life. In neither of these instances is there any possible chance for the physician to change the situation.

As to therapy, so far as the symbolism is concerned, that is all very interesting but it doesn't help one very much. What the patient needs is someone in whom he has enough confidence—whether he will do it at the end of one hour or the end of one year—to tell his story and what

ails him. Direct pressure from the outside may fail in this. It is something that must come from the inside, a spontaneous deliverance. I am not at all sure that it is always physicians that are going to cure many of these patients. They need restoration of confidence, peace, and some faith, perhaps religious faith, that we as doctors are not necessarily the ones to give.

DR. WALTER C. ALVAREZ (Rochester, Minn.): I should like to say a word of appreciation of Dr. Bond's paper and of the officers for their good sense in having a talk like this on the program. We ought to have one or more every year, because there is no question that we do not always recognize insanity in our patients. For instance, recently a physician sent me a patient with a letter stating that the woman had an amebic diarrhea which wouldn't clear up with treatment. He apparently had not noticed that the real trouble with the woman was that she was in a spell of melancholia. He had been hunting, as most of us do, for a physical disease in the abdomen to explain a disease of the brain. The woman has since attempted suicide, and when I last heard of her she was where she belongs, in a hospital for the mentally unbalanced.

Every year I see patients who have been operated on time and again for a supposed intestinal obstruction which is not found; why? Because it is in the woman's mind. As I grow older in the practice of medicine I hope to develop more skill in differentiating two types of nervous patients: one, the type that I can help because they are primarily sensible, tractable, teachable and cooperative people who are tired, hypersensitive, nervous and upset because of a long period of overwork or strain or unhappiness. These people will make an effort to get well, and with rest and sedatives and a proper understanding of their trouble, they will usually pull out. I am happy to give these people all the time they need because such time is usually well spent, and in many cases I am later rewarded by learning that the patient is well. The other type of patient we can often recognize from the start. Sullen and uncooperative, or too stupid or undisciplined or psychopathic to cooperate with the physician for more than a few hours at a time in an attempt to reform bad habits, or obsessed by fears or crazy ideas, or too queer to mix with their fellows, what can one hope to do for them? Usually we waste what time we spend trying to help them.

I have little use for psychoanalysis, because so often one begins with a congenitally psychopathic person and ends up with one. To show what I mean, let us take the case of William Ellery Leonard, who can't go 50 feet from his house because of an agoraphobia. He tells in his book "The Locomotive God" that he was psychoanalyzed by several experts and that they dug out the cause of the trouble, a fright when he was four years old. They brought this fear out in the open, and according to Freud he should be well, but he isn't. He still can't go out.

DR. EARL D. BOND (Philadelphia, Pa., closing the discussion): I appreciate very much the sympathetic reception which this paper has had. You might have objected to many parts of it.

I was interested in Dr. White's statement that these psychological patients came to the psychiatrist first. I had understood that of psychotic patients, a certain few were in mental hospitals and the rest were about consulting gastro-enterologists and internists as to why their gastro-intestinal symptoms made them feel as they did.

On the other hand, Dr. White's question as to what should be done by the gastro-enterologist, was answered beautifully by Dr. Schindler, and I should like to associate myself with everything that he said. I take it that emotional factors often turn out to be very practical ways of handling some gastro-enterological disturbances. It is often the internist who gets a chance to deal with the emotional factor just, so to speak, as it is hovering over

*v. Bergmann: G. Zum Abband "Organneurosen" als Folge Interner Diagnostik. *Deutsch. Med. Wo.*, 53:49, 1927.

the gastro-intestinal system and ready to settle into it. Now, the way the physician who is dealing with the gastro-intestinal upset handles that critical situation may determine the onset or the prevention of a long neurosis.

The psychiatrist is likely to get to most of these things second and third hand, and so is handicapped.

In the matter of symbols and what they mean, the psychiatrist would ask this of internists: Isn't there something in your own study of the personality as you come to it without prejudice that will help in the understanding of symbolization, and of the importance of the emotional element in gastric and intestinal disturbances?

Studies on the Use of Aluminum Hydroxide Gel in the Treatment of Peptic Ulcer

By

EDWARD S. EMERY, Jr., M.D.

and

ROBERT B. RUTHERFORD, M.D.

CLINICAL experience teaches that one can divide patients with gastric and duodenal ulcer into 3 groups, depending upon the severity of the disease: the mild, moderate and severe. The mild and moderate cases do well with any good medical or surgical regime. The severe cases present a serious therapeutic problem because they respond unsatisfactorily to both medical and surgical treatment.

Of the severe cases, patients with hypersecretion present the greatest problem in therapy. Not only does the stomach secrete a large amount of highly acid juice during the day, but the empty stomach is prone to secrete large quantities of acid at night. Because it has been shown by Mann and Williamson (1), Matthews (2) and others (3) that the free hydrochloric acid is an important factor in the development and chronicity of an ulcer, it is obvious that strict neutralization of the gastric juice will give the best opportunity for healing to occur. Although Sippy designed his regimen to produce complete neutralization, the treatment may not accomplish this objective in the patient with a hypersecretion, for the following reasons:

1. The tendency of the stomach to respond to alkali by an increased secretion of acid reaches its peak in the presence of a marked hypersecretion.

2. Secretion continues during the night in many instances and prevents healing.

3. The onset of alkalosis as a result of the large amount of alkali which may be required.

Therapeutic efforts are defeated frequently by failure to obtain complete neutralization of the gastric juice before the patient is in alkalosis, and by the return of an uncontrolled secretion after the alkalosis has disappeared. The surgical results in this group of patients are unfortunate. Jejunal ulcers and other undesirable effects are prone to follow all types of operative procedures.

In 1929, Crohn (4) stated that colloidal aluminum hydroxide is an effective antacid, that it reduces total acidity to a point where complete cessation of subjective symptoms is almost an invariable rule and that it is non-absorbable and non-toxic. He found that it produced prompt relief from pain and heartburn in cases of functional hyperacidity and gave almost immediate relief from peptic ulcer distress in twenty

patients whom he had studied. Others have confirmed these statements. Einsel and Rowland (5) report that after three weeks of treatment the hyperacidity of peptic ulcer is reduced to normal or subnormal levels. Also, it has been stated (6) that the secretion of acid does not return to former levels for several weeks after the discontinuance of the aluminum hydroxide. A preparation which can neutralize the gastric contents and decrease the production of acid should be useful in controlling hypersecretion.

However, the literature provides little information on the type of ulcer case which has been treated. One would like to know whether aluminum hydroxide can control those patients who respond unsatisfactorily to our usual therapeutic measures.

The object of this paper is to present some observations on the action of colloidal aluminum hydroxide in the severe type of case.

PRESENTATION OF DATA

To date, we have started treatment with colloidal aluminum hydroxide on 21 patients. Fourteen were admitted to the wards of the Peter Bent Brigham Hospital, to whom the medication was administered by the constant drip method, as described by Woldman and Rowland (7), for one week and then orally in hourly doses. Seven patients were started only by the oral method in the Out-Patient Department and were ambulatory from the beginning. All these patients had proved resistant to past treatment. Twelve patients represented the most severe type of case for one or more reasons. Nine fell into the group of the moderately severe. Eleven of the severe cases had a marked hypersecretion, in 8 of whom the gastric contents were never controlled satisfactorily by one or more treatments on the hospital wards with the Sippy regime. Four had never been hospitalized for economic or social reasons and had not responded to an ambulatory treatment. Four of the most severe type had suffered a previous perforation. One of these had had a gastric ulcer and later a duodenal ulcer perforate. Five had had previous surgery, two of whom were left with a jejunal ulcer and the other three continued to have severe pain. The situation of one of the severe cases was complicated also by nephrolithiasis.

Seven were classified as moderately severe because

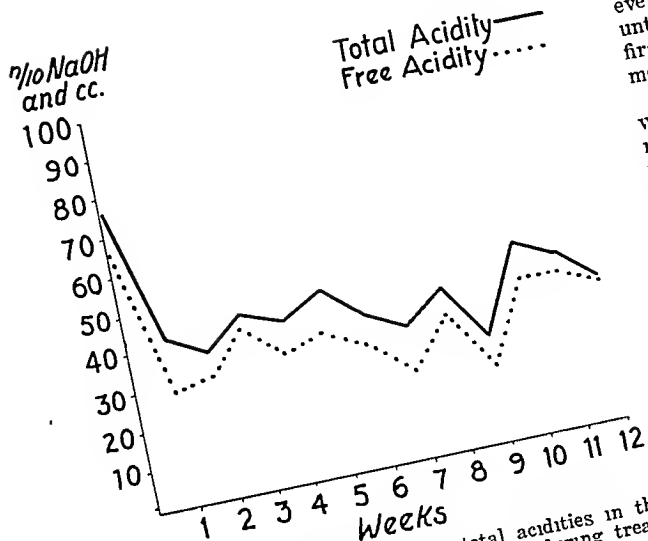


Chart 1. The average free and total acidities in the gastric contents of 12 patients before and during treatment with colloidal aluminum hydroxide.

they continued to be bothered by symptoms although following a good ambulatory treatment.

We were able to obtain satisfactory data on only 12 patients, five of whom were treated by the drip method and seven by the oral method. Several patients refused to continue the treatment because they objected to the tube, or to the taste of the material. A number of others would not come in for gastric analyses although they were satisfied with the results and continued with the treatment. Eight of the twelve patients on whom we have data were in the "severe" group and four in the "moderately severe" group.

The routine has been as follows: A gastric analysis was performed on all patients before the onset of treatment. The analyses were repeated at weekly intervals on nearly all cases. The aluminum hydroxide was omitted for 24 hours before the analysis to avoid any immediate effect. The same method was used each time; that is, a Levine tube was passed either nasally or orally and the fasting contents removed. Fifty cc. of an 8 per cent alcoholic solution was then injected into the stomach and 10 cc. specimens taken at intervals of 20, 40, 60, 90 and 120 minutes. An injection of $\frac{1}{2}$ cc. of histamine hydrochloride, 1-1000 solution (the equivalent of $\frac{1}{2}$ mg) was then injected and the gastric contents allowed to syphon off for one hour. All titrations for free and total acidity were done in the usual way with Topffer's solution and Phenolphthalein as indicators. Those patients who started on the drip method were shifted to the oral method after one week. The preparation known as Creamalin has been used through the courtesy originally of the Cleveland Chemical Associates and later of the Albap Pharmaceutical Co., Inc.

A solution of one part of the aluminum hydroxide (Creamalin) to 3 parts of water was used at all times. The amount which was used varied slightly, but on the average 15 drops per minute were allowed to drip through the tube. It was given orally in amounts of 60 cubic centimeters of the mixture per dose. A dose was given every hour from 8 a.m. to 9 p.m.

In addition to the aluminum hydroxide, the patients were fed according to the schedule outlined by Sippy. They received 90 cc. of equal parts of milk and cream every hour and feedings were gradually introduced until 6 small meals were being taken at the end of the first week. The 6 small feedings were changed to 3 moderate-sized meals after 3 weeks.

All patients were relieved of their ulcer distress within 24 hours and had no recurrence of pain while remaining on the treatment. Several patients stated that their stomach felt "easier" under the aluminum therapy than with the alkaline powders. The only complaint of those who have followed the treatment has been severe constipation in some instances. Nearly all the patients have had to take some mineral oil and some have been troubled in spite of large doses of oil. Our studies show that the colloidal aluminum hydroxide is a satisfactory antacid if given in large enough doses. Tests were made for the presence of free acid at numerous times throughout the day and at varying intervals during the course of treatment. No free acid was found at any time during the day while the aluminum was being administered.

In addition to its neutralizing the secreted acid, we have confirmed the fact that it decreases the titratable acidity of the gastric juice. Chart 1 shows the effect on the titratable acidity of all patients over a period of 12 weeks, by recording the highest readings obtained with the alcohol meal. The free acidity dropped from an average of 68 before treatment to approximately 35 after treatment. The total acidity has followed closely the free acidity in all instances. Its drop is rapid on the drip therapy and reaches its low point by the end of the first week. Our experience shows that a week is required for the acid to reach its lowest level and that a continuation of the drip beyond this time does not cause any further decrease in the titratable acidity. Oral administration of the drug produces a somewhat slower decrease in the titratable acidity which ultimately reaches the same general level.

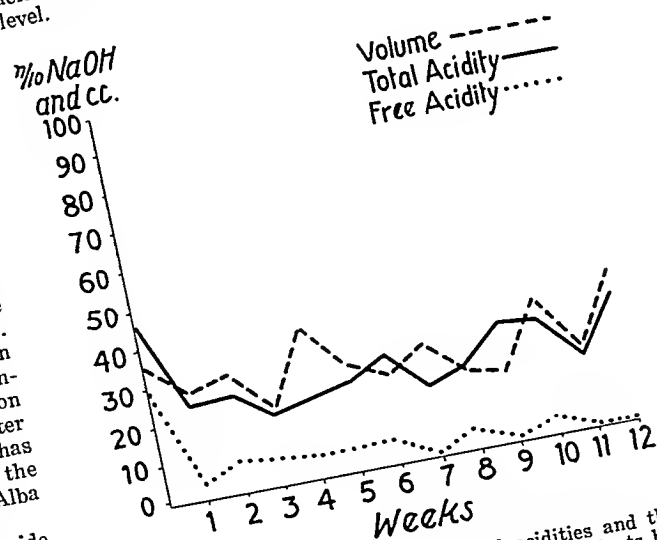


Chart 2. The average free and total acidities and the average volume of the fasting contents of 12 patients before and during treatment with colloidal aluminum hydroxide.

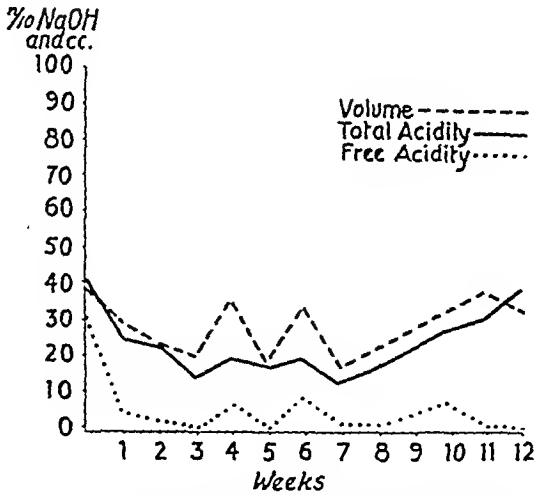


Chart 3. The average free and total acidities and the average volume of the fasting contents in five patients to whom aluminum hydroxide was administered through a Levin for one week and afterwards by mouth.

The effect on the fasting gastric contents is shown in Charts 2, 3 and 4. There was little change in the volume of juice. However, the treatment resulted in a definite drop in the free acidity approaching an achlorhydric condition in many instances. Studies on the fasting contents also demonstrated that the free acidity drops more slowly in response to the oral therapy than if the patient is started on the drip method. It required about 3 weeks for the free acidity to reach the same level in the oral cases as occurred in the drip cases, at the end of the first week.

The free and total acidity decreased in response to stimulation by histamine. However, histamine resulted in a greater volume of juice after treatment with colloidal aluminum hydroxide. The volume averaged 98 cubic centimeters before treatment was instigated and gradually climbed to 120 cubic centimeters at the end of 10 weeks. (Chart 5).

DISCUSSION OF DATA

It is evident that colloidal aluminum hydroxide is an effective drug for controlling gastric acidity. It has been possible to neutralize and to maintain complete neutralization in every case. Furthermore, it decreases the acidity per unit volume of gastric juice. This has been found in all the specimens studied whether fasting, after alcohol, or after histamine. However, the results with histamine suggest that the treatment may not affect materially the amount of acid secreted. Because of the greater volume, the total amount of acid which was secreted by these patients after histamine was only slightly less than before aluminum hydroxide was given. (see Chart 6). We have no data which will explain the increased volume. The total solids in the gastric juice are apparently the same before and after treatment. The figures for our cases are as follows: Total solids before treatment and after alcohol were 0.544 grams per cent. After one and a half months of treatment they were 0.572 grams per cent following alcohol and 0.535 grams per cent after histamine. Likewise, the amount of protein

in the juice was similar before and after treatment. We have no data on the total base, but Adams, Einsel and Meyers (6) state that the values are closely correlated by an inverse relationship to the figures for free and total acid concentration. This may explain why there is an increased volume with a decreased amount of acid per unit volume.

We were interested particularly in discovering how treatment with aluminum hydroxide affects the condition known as hypersecretion. Of the 11 patients with this condition, 7 were relieved of all symptoms within 24 hours upon administering the aluminum by the drip method. Six of these patients had failed to obtain complete relief with the Sippy regimen. In addition to the aluminum producing prompt relief, it decreased effectively the free acidity in the fasting contents, as determined at the time of the gastric analysis. The same effect was found upon samples obtained from the stomach at midnight. The free acidity which averaged 39 units before treatment dropped to an average of 11 units after treatment. In two patients the free acidity averaged 5 units five months after treatment was begun. However, the volume of the night aspirations did not change. The average volume before treatment was 98 cubic centimeters and later was 106 cubic centimeters.

Four patients with a hypersecretion were treated in the Out-Patient Department. All of them were more comfortable than before the aluminum was started. One of them was enabled to continue actively his work as a dynamiter although he was unable to work at the time he consulted us.

The evidence which has been cited makes us believe that colloidal aluminum hydroxide is indicated in the treatment of the patient with a hypersecretion, a night secretion, or both. It is advisable to administer the aluminum hydroxide by the drip method at the start. This ensures complete neutralization of the gastric juice at all times throughout the 24 hours. In this way, the ulcer is freed almost immediately from the harmful effects of the hydrochloric acid. The rapid

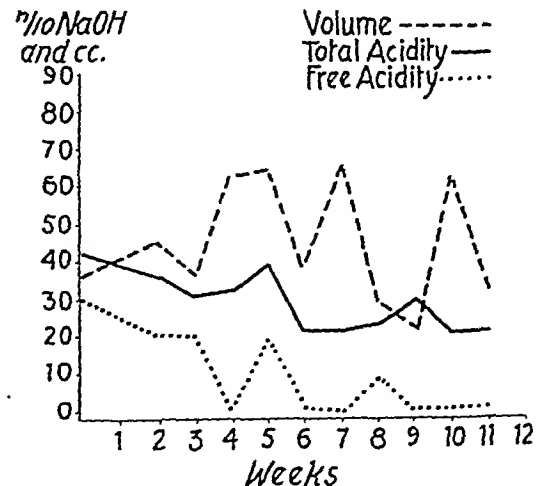


Chart 4. The average free and total acidities and the average volume of the fasting contents in seven patients to whom aluminum hydroxide was administered by mouth from the beginning.

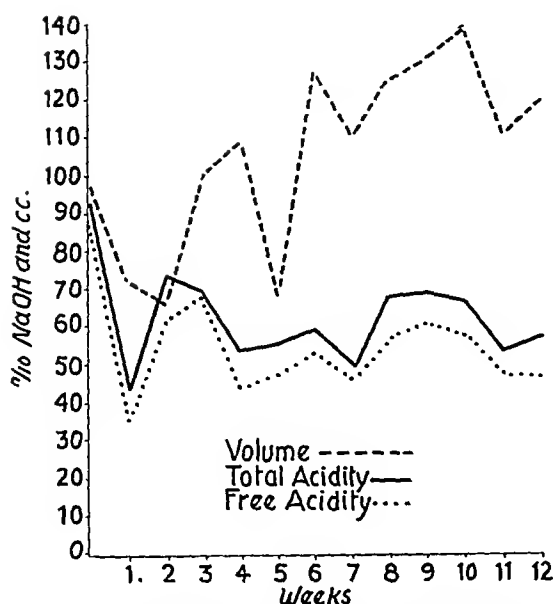


Chart 5. The average free and total acidities and the average volume of the gastric contents in response to 0.5 milligram of histamine. These figures were obtained from the total amount of juice which siphoned off the stomach in one hour.

relief from pain at night permits complete rest and ensures for the nervous patient, an opportunity to relax.

Furthermore, it is our opinion that all patients who fail to respond satisfactorily to the Sippy regime should be treated with aluminum hydroxide before resorting to surgery. At present, there is a tendency to advocate radical surgery for this type of patient. This is an admission that the older and simpler operations have not proved satisfactory. However, the present reports on subtotal gastrectomy do not tell us whether the final results will be superior to the simpler operations. The use of subtotal gastrectomy is comparatively recent in this country. It is to be remembered that one cannot accurately evaluate any form of treatment in peptic ulcer until a large number of patients have been carefully followed for five years or more. Although at the Peter Bent Brigham Hospital, we have been conservative in the use of this operation, we have encountered already, a few patients in whom a recurrence of ulcer has followed almost complete removal of the stomach.

Therefore, we believe that it is distinctly worth while to try aluminum hydroxide before attempting a subtotal gastrectomy. In 1934 (8), one of us stated the belief that it was preferable to treat these severe cases by medical means even though the results were somewhat unsatisfactory, rather than to submit a patient to the danger of a jejunal ulcer. The present evidence on the effect of colloidal aluminum hydroxide suggests that these patients can be carried along more satisfactorily by medicine than formerly. Certainly, it seems probable that hypersecretion may be kept under control as long as adequate amounts of the aluminum hydroxide are administered.

Postoperative jejunal ulcers have always been a

problem to our clinic because they have responded less well to therapy than the original ulcer. Two of the patients treated in this series had a jejunal ulcer and both have appeared to do better with the aluminum therapy than with the usual alkaline powders. Therefore, we look forward to studying the effect of aluminum hydroxide on this type of case more fully in the future. One of our patients had a marked retention which had been present over a considerable period of time. He was placed on the drip therapy for a period of three weeks with a decrease in the retention from 2300 cc. to 100 cc. This observation is of importance because one of our problems has been the treatment of obstruction in the presence of a hypersecretion. If medical treatment fails to control the acidity there is slight chance of improving the obstruction and surgery must be resorted to, with its ever present danger of a jejunal ulcer. The fact that treatment by aluminum hydroxide can overcome obstruction may relieve the physician's mind of the necessity of having to advocate surgery. Moreover, if one encounters patients whose obstruction does not respond to therapy, it will be possible to overcome the hypersecretion before attempting surgery and perhaps, by this means, can prevent or decrease the probable development of a jejunal ulcer.

Colloidal aluminum hydroxide is also useful for treating ulcer patients who show a tendency to form renal calculi. The drug is absorbed but slightly and does not interfere with the acid base balance. It proved to be very useful in treating the four patients of this series who had nephrolithiasis.

These studies show that colloidal aluminum hydroxide is a useful therapeutic agent in the treatment of peptic ulcer. It has three advantages:

1. Complete relief of pain is obtained within a short time after the onset of treatment.

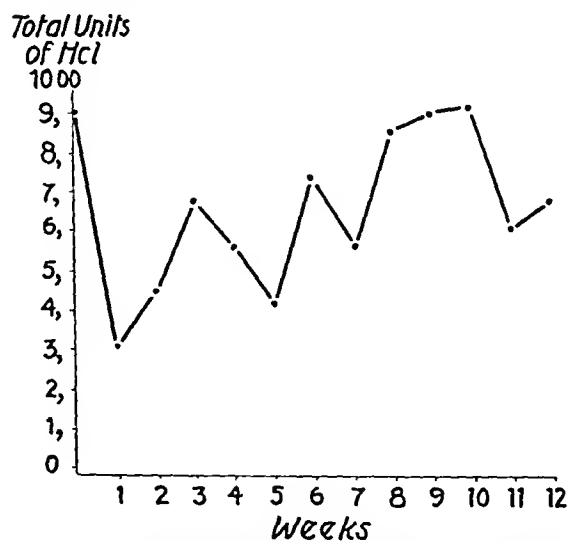


Chart 6. The average number of units of hydrochloric acid secreted in response to histamine, by 12 patients, before and after treatment with aluminum hydroxide. These units are the product of the total acidity per 100 cubic centimeters of gastric juice, in terms of tenth normal sodium hydroxide and the volume of the gastric juice in cubic centimeters.

2. Complete neutralization of the gastric juice can be obtained in all patients.

3. It is not known to interfere with the general bodily chemistry.

Because its present cost is greater than the alkaline powders usually prescribed, one may wish to limit its use to specific indications. Furthermore, the question arises of why the drug inhibits the secretion of acid, and how long it is justifiable to use it in the individual case.

From the data presented by others there would seem to be no contraindication to its use so far as its absorption and effect on other organs is concerned. We have submitted two patients to operation after the use of the aluminum. One was a patient on the Surgical Service of the Peter Bent Brigham Hospital, to whom, with the permission of the surgeons, we gave the aluminum hydroxide drip for a period of 4 days before operation. The other was the patient with obstruction who had received the treatment for three weeks. Although he was improving, he desired surgery and because we were interested in observing the effect of the aluminum on the gastric mucous membrane, surgery was performed. Both had resections done and the gastric tissue studied histologically. No change could be seen in the gastric tissue.

SUMMARY AND CONCLUSIONS

Twelve patients with peptic ulcer have been treated by colloidal aluminum hydroxide. This was given orally or by a combination of a continuous drip and oral method. It was found that the gastric contents can be neutralized completely by this therapy. Relief of pain occurred within 24 hours. In addition to neutralizing the secreted acid, the drug decreased the titratable acidity. Patients with a marked hypersecretion were brought under satisfactory control. No adverse effects have been noted by the treatment. It is suggested that this form of therapy will be useful particularly in treating patients with a marked hypersecretion who formerly have been difficult to control by the usual alkaline powders.

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DISCUSSION

DR. ALBERT F. R. ANDRESEN (Brooklyn, N. Y.): It was interesting to see how the speaker proved so conclusively that gastric acidity can be reduced by his method. However, it may be interesting to consider the relation between hyperacidity and ulcer.

Hyperacidity is undoubtedly not the cause of ulcer, because it is found in patients without ulcer and during the intervals between the occurrence of ulcers.

Hyperacidity does not interfere with the healing of ulcer, as we know from animal experiments showing rapid healing in the presence of acid, from observations in humans not treated by neutralization of acid and from the

X-ray proofs submitted to this Association by Lewis Gregory Cole several years ago, showing rapid and complete healing of ulcers without any treatment.

Hyperacidity is not the cause of pain in ulcer, as we know from the fact that pain does not occur during fractional gastric analysis when the high point of acidity is reached, but does occur when the stomach is empty or nearly empty and with reduced acidity from the fact that pains can be relieved if the patient takes acidified drinks in sufficient quantity to allow hunger contractions, and from the fact that pains do not occur during the intervals between ulcers, when the hyperacidity is still present.

Hyperacidity, therefore, not being a causative factor in ulcer, not being a cause of pain in ulcer and not interfering with the healing of ulcer, need not be considered in treating ulcer cases. Besides, an efficient neutralization of acid might conceivably interfere with digestion and with hormonal stimulation. I feel therefore that while the speaker has proved his point that acidity can be reduced by his method, its value in ulcer is not thereby proved.

DR. V. C. ROWLAND (Cleveland, Ohio): The aluminum hydroxide drip treatment in our hands has proved to be a procedure of definite value, especially for the case that does not respond to ambulatory treatment, as a special therapy before surgery and in the occasional case of recurrence after operation. By the use of the collapsible tube the discomfort is reduced to a minimum and on account of the valve-like action the flow of the aluminum hydroxide suspension is uniform and quite independent of gagging or straining on the part of the patient or any change in intragastric pressure. Only the occasional highly nervous patient has difficulty in retaining the tube for a ten-day period. Rather liberal use of sedatives and antispasmodics undoubtedly is of distinct help in the healing of ulcer as well as facilitating the use of the tube.

Pyloric obstruction from edema or spasm may be handled at first by the use of the Levin tube and, at intervals, the Wangenstein aspiration for removing retained gastric contents. The aspirating unit may be joined to the drip unit by a Y tube so that the flow can be reversed as often as is necessary to relieve nausea or distress. In this way much of the spasm and obstruction is relieved in a few days, and usually before the end of the week the collapsible tube may be used to replace the less comfortable Levin tube.

In hemorrhage cases the drip treatment has been instituted immediately on admission to the hospital or after transfusion and other emergency treatment. This is done with the idea of preventing acid digestion of a newly formed clot and recurrence of bleeding. Regular bland feedings are used at two hour intervals, thus enervating out the principles of Meulengraet plus the added principle of continuous neutralization. Vitamin C is also used in full dosage. The results in hemorrhage cases have been very good.

In suspected malignancy the tube treatment provided a more precise and expeditious therapeutic test than the routine management. This, of course, applies only to cases with a slight suspicion in which a second X-ray is in order after one therapeutic test treatment, and in no sense to take the place of surgery when there is a clear indication. A recent case in which the suspicion of malignancy remained in the X-ray after a ten day use of the tube treatment, but which proved to be a benign induration after resection showed advanced healing over the crater of the lesion. The deformity in the X-ray was largely due to the inflammatory thickening which radiated from the site of the ulcer for an inch or an inch and a half from the crater which was covered with epithelium.

The drip treatment, of course, cannot prevent recurrences or produce any more permanent results than are implied by a more complete degree of healing at the end of a period of continuous neutralization.

Like all other procedures it needs to be properly evaluated and to be used with discretion and individualization.

DR. VICTOR C. MYERS (Cleveland, Ohio): I was quite interested in Dr. Emery's remarks and think from our experience, I can agree with them, I have a few remarks I might make about aluminum hydroxide itself which may be of some help.

As a result of a paper which was presented a few years ago, we were called upon a number of times to suggest where one might obtain a satisfactory preparation of aluminum hydroxide. Personally I do not like to recommend a product not accepted by the Council of Pharmacy and Chemistry of the American Medical Association, and at present no product has been accepted. I am reasonably sure the Council would be glad to accept a product submitted to it under the name of colloidal aluminum hydroxide, without a trade name and without any false therapeutic claims.

We have recently examined a number of different preparations. To put them on a common basis, we have determined the total solids and then calculated the sodium chloride contents from the chloride titration. If one subtracts the weight of the NaCl from the total solids the residue should be aluminum hydroxide. If the preparation is a good one, the titrable acid combining power should equal the theoretical acid combining power calculated on the basis of the aluminum hydroxide (total solids less NaCl).

Apparently there are a good many preparations that do not yield the full acid combining power. If you heat a preparation of aluminum hydroxide for a few minutes, you will destroy most of its acid combining power. Granting that the value of aluminum hydroxide therapy is not entirely dependent upon its antacid properties, it should, nevertheless, have a theoretical acid combining power.

The reason for the titration of chloride is that the most logical method of preparing aluminum hydroxide is from aluminum chloride and sodium carbonate. The result of the chemical reaction should be aluminum hydroxide, some carbonic acid gas, and sodium chloride. It is simply necessary to wash out the excess of sodium chloride to obtain a satisfactory preparation of aluminum hydroxide.

A solid content of 5 to 6 per cent furnishes the best consistency, since the gel does not settle out. One of the preparations we examined had a lower solid content. It settled out, and was again evenly suspended only after considerable shaking. More uniform dosage is obtained when the gel is stiff enough to hold its consistency.

There are a number of preparations on the market, but it seems to me they all cost too much. For an eight-ounce bottle the ingredients cost about ten cents, and as you know the market price is very much more than this. The market price is unnecessarily high. I hope that these remarks may be of some help.

DR. ANDREW C. IVY (Chicago, Ill.): I think it might be appropriate here to summarize in about two minutes the results that we have obtained by treating Mann-Williamson dogs with aluminum hydroxide on a diet of parboiled meat, milk, and bread. This curve (using the blackboard) will represent the time of death with ulcer. We will say at this time 50 per cent of the dogs were dead of ulcer at ten weeks. That is a curve using forty dogs. If we give the animals a special diet of the same foods I mentioned, plus ground pancreas, liver, and syrup, we get a curve that is flatter, like that.

We took approximately twenty dogs on this special diet, and we gave them aluminum hydroxide four times a day, in the morning, at noon, about six o'clock at night, and about eleven o'clock at night. We found that the dose of aluminum we gave produced neutralization of free acid for a little longer than an hour on that regime, and our curve was about like that.

The early part of the curve was higher and the latter part a little lower than the control. There was not a great deal of difference.

We thought that we might obtain better results if we

gave a dose of aluminum hydroxide every hour, so as to assure complete neutralization of free acid; so we medicated the dogs every hour from seven in the morning until seven at night and gave a dose at ten o'clock and at midnight, and our survival curve was like that (laughter); in other words, the administration of the aluminum hydroxide cream took away the beneficial effects of the special diet, and we thought that that might be due to the possibility that the aluminum hydroxide was inactivating some enzymes in the pancreas, because a Mann-Williamson dog suffers a pancreatic deficiency. We studied that and found the aluminum hydroxide did not interfere with the enzyme action.

What we believe happened is this, and this is the prime suggestion which comes out of our work: We would not conclude that aluminum hydroxide therapy is of no value in the treatment of peptic ulcer in man from this work, but we would conclude that aluminum hydroxide is contraindicated in the presence of biliary or pancreatic deficiency on the basis of this theoretical consideration. When aluminum hydroxide interacts with acid in the stomach, aluminum chloride is formed, and we know that aluminum chloride is irritating to the intestine. Normally it would be reconverted to the hydroxide or an insoluble aluminum compound if plenty of alkali is present but, if not, then the aluminum chloride will irritate. There is another thing we must keep in mind in this type of therapy, that is a finding which the Remsen board seemed to agree on, namely, that aluminum increases the phosphate loss in the feces.

We are at the present time trying out an aluminum phosphate cream to see what it does. We have obtained results on only two dogs so far, but the results are encouraging; but, you can't get encouraged or enthusiastic about the results on two dogs any more than you can on two patients.

DR. HENRY A. RAFSKY (New York, N. Y.): I am inclined to agree with Dr. Andresen in his concept that the acidity does not play such an important role in the treatment of peptic ulcer. One year ago, before this society, I stated that the secretory response in peptic ulcer was a better diagnostic index than a therapeutic guide. I have studied the histamine response in ulcer patients when they first came to the hospital, before any therapy was tried and again just before they left the hospital. I did not see any material difference in the acid curves when the patients had severe symptoms and when they became symptom free. Being a protégé of Dr. Max Einhorn, I have observed for many years the results of treating ulcer patients with duodenal alimentation, in which practically no attention was paid to the acid factor. Excellent results were noted in most of these patients when they were hospitalized and treated by this method. Patients with hemorrhages as well as those with inflammatory pyloric obstruction were also treated with the duodenal tube.

In reference to Dr. Emery's statement regarding the volume of the gastric secretion, I wish to state that in comparing the acid curve and volume of the gastric secretion in normal individuals with high acidity and in patients with peptic ulcer, I noticed the following: In the normal patients the acid curves were high but the volumes were low. In ulcer patients the acid curves were high and the volumes were also correspondingly increased. Dr. Emery observed a high volume in his patients after treatment. This, I think is the crux of ulcer treatment, for unless we find some therapeutic measure which will keep the volume of the gastric secretion down in ulcer patients, we have not struck at the basic principle of ulcer therapy.

DR. MARTIN E. REHFUSS (Philadelphia, Pa.): Everybody is trying the blackboard, so I think I will try it, too. I noticed that the whole discussion this afternoon has resolved about the question of acid; in other words, the control of acid. The control of acid implies the ab-

normal formation of acid or at least acid as the cause or principal factor in the further formation of ulcer.

I would be very certain to follow these things if it were not for the fact that we spent, Dr. Hawke and a number of chemists and myself, some eight years in studying the acid curves of normal people. We had two hundred normal men. We studied the acid curves of two hundred normal individuals, and we found there is a tremendous normal variation in acid.

About 40 per cent have relatively high acid and a tendency to hypersecretion, and 35 per cent of normal individuals between twenty and twenty-five have a relatively low acid output. I personally believe that the acid response of an individual is as characteristic of that individual as the nose on his face.

I don't believe—and we found repeatedly, that we could control this free acid in the treatment of ulcer—we could control it with this drip and with kaolin and with alkalis, and the greatest combining substance of all is food, but there are only about twenty different diets for the control of ulcer, and it is a chronic disease, and if you keep them on an unbalanced diet too long, you are likely to get avitaminosis.

In the first place, we believe that the cause of ulcer is not acid but the cause of ulcer, like cirrhosis of the liver, must be a sensitization of the gastric cell by something.

All our experimental work shows that first cell death and then digestion and erosion by acid. The patient comes to us because he has an ulcer. He wants that ulcer healed. He doesn't want his secretion altered, necessarily.

Anything that will control the secretion long enough to permit that ulcer to heal is the logical thing.

At Jefferson we have been using in the wards this drip and we have been checking them very carefully and we have had very good results for the period in which the drip was used. We have kept it as long as eighteen days. We have succeeded in healing enormous ulcers insofar as the demonstration of the lesion by X-ray examination and in one or two instances by gastroscopy revealed. In the intervening period this method served to control the lesion, but my experience shows in all probability two or three weeks later they will revert back to their individual type of secretion; therefore, I feel if this method is used for two, or three, or four weeks in gastric ulcer especially (you don't see the same changes in duodenal ulcer), this method, if it will control the situation so the original area of necrosis or whatnot can be healed, then it has done the work which it was intended to do and for that reason I, for one, believe we can't expect a change in the secretory output of an individual.

In our experience healing does take place with this method.

DR. BURRILL B. CROHN (New York, N. Y.): I have no personal experience with the aluminum hydroxide drip as a method of treatment for ulcer, but I should like to ask Dr. Emery why the principles of Dr. Winkelstein's milk drip do not answer all the requirements represented by the aluminum drip; has not the milk drip the same value of neutralizing acidity, day and night, and doesn't it cover in addition the nutritive requirements of an ulcer patient on a minimum diet? Does it not answer the criticisms of Dr. Ivy insofar as there is no possible secondary or byeffect of the breakdown of aluminum hydroxide into aluminum chloride?

From the experience I have had with the milk drip, it

answers all these and gives satisfactory results. I do not suppose it alters eventually the acid curve any more than does the aluminum hydroxide.

For years it has been known that the ulcer patient's secretory curve is not altered. Nothing alters his acidity curve which is characteristic for the individual. During the course of treatment the ulcer heals under an anacid substance. It heals, though the acid may persist.

I should like to ask Dr. Emery if he has experimented with the milk drip and whether he feels that the aluminum hydroxide has any advantage over the milk drip for the same purpose?

DR. EDWARD S. EMERY, Jr. (Boston, Mass., closing the discussion): I think I will answer Dr. Crohn first. I don't know that it has any advantage over the milk and soda drip. Personally I have not used the milk and soda drip. We tried this out because it has been reported that the secretion of hydrochloric acid remains lower than before treatment, for several months after the treatment was started. If that should be true, which I don't know about, because we haven't had an opportunity to study that point ourselves, then we have a method which will accomplish something which the milk and alkaline drip does not. But I can't answer Dr. Crohn's question.

The rest of the discussion seems to come down to the relationship of hydrochloric acid to ulcer.

It seems to me that it is perfectly clear. On the one hand, there is evidence that the acid doesn't change with the periods of activity and periods of quiescence of an ulcer. If that is true, then there must be some other factor in addition to the acid, otherwise a normal stomach would be digested by its own acid. On the other hand, we have the evidence as ably presented by Lindau and Wulff, and others, that if hydrochloric acid strikes tissue which doesn't usually receive it, then a peptic ulcer develops. Therefore, it seems to me we have conclusive evidence that hydrochloric acid is related to a peptic ulcer in some way.

Finally, the question of the Mann-Williamson dogs—I think there has been a lot of misunderstanding about that. Mann and Williamson went out to prove or disprove the relationship of hydrochloric acid to peptic ulcer, and that is what it seems to me they did do. They were able to show that unneutralized hydrochloric acid resulted in a peptic ulcer in an animal, but that if you neutralized the hydrochloric acid, the ulcer did not develop. They didn't try to say that that was the mode of production of an ulcer in a human being, and certainly we have got a great deal of evidence, or at least we know that the procedure of the Mann-Williamson operation does a great deal more than just result in an unneutralized gastric juice. Hence, it seems to me, that all the literature, or all the data we have at the present time makes it pretty clear that something happens to break down the normal resistance of the mucous membrane to hydrochloric acid.

I don't know personally whether this treatment is going to be of any more value than the means of producing rapid relief, as Dr. Rehfsuss has just said. I think it is useful because we have been able to bring patients under control, in the way of relieving their pain more rapidly and in a more comfortable way than we have been able to do with any other kind of treatment. If it serves nothing more than to take care of the patient until such a time as the normal healing process is accomplished through adequate diet and general good hygienic treatment, then I think it may prove useful.

The Level of Ascorbic Acid in the Blood and Urine of Patients with Peptic Ulcer*

By

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and

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SINCE 1935 the literature has contained numerous articles dealing with the metabolism of Vitamin C. The majority of investigators (2, 6, 7, 10) finding a lower than normal excretion and blood level of ascorbic acid in a group of patients, have adopted the view that a deficiency of Vitamin C was present in these cases. In fact, it has been assumed that a state of asymptomatic scurvy is present in patients with peptic ulcer because of the low excretion levels found. In this connection it is worthy of note that Finkel (5) found the excretion of ascorbic acid to be low in a group of hospital patients with different conditions, but was unable to correlate this finding with any clinical phenomenon. Rivers and Carlson (4) found that in cases of hemorrhage from the gastro-intestinal tract, the ascorbic acid levels in blood and urine were low. They pointed out that the customary diet given to patients with peptic ulcer is likely to be deficient in Vitamin C. Lazarus (10) found Vitamin C deficiency in a group of fifteen patients with peptic ulcer, thirteen of whom had a history of bleeding or were bleeding on admission to the hospital. However, a smaller number of non-hemorrhaging patients also had low ascorbic acid levels of blood and urine.

The purpose of this study was to gain more information concerning this apparent deficiency and to ascertain the amount of additional ascorbic acid necessary to maintain normal levels of excretion in patients with peptic ulcer.

It has been the policy of the Gastro-Intestinal Department of the Lahey Clinic to give orange juice to patients in the hospital for ulcer management. These patients receive two ounces of orange juice diluted with six ounces of water in divided amounts throughout the day. No cases of clinical scurvy have been noted in patients on this regimen. All the patients received hourly doses of an antacid, either colloidal alumina gel (amphojel) or tri-basic calcium phosphate (tricalate).

By our methods, the twenty-four-hour urine excretion of ascorbic acid in normal individuals was found to be from 17 to 25 mg. per cent. These values are in keeping with those reported by others (2, 3, 4, 5). Analysis of the first morning urine specimen has been shown to equal $\frac{1}{4}$ to $\frac{1}{8}$ of the twenty-four-hour amount. This appeared to be a relatively constant fraction of the total twenty-four-hour excretion, so as a matter of convenience was used in this study. Blood for ascorbic acid analysis was taken from patients in the fasting state. The methods employed for urine analysis were those described by Harris and Ray (2) and that for blood by Farmer and Abt. All analyses

were carried out as soon as possible after the sample was secured. In all, 808 estimations were made on 264 patients.

The blood Vitamin C was estimated in twenty-seven cases of peptic ulcer. In many of these patients, the analyses were done daily for the period of a week in order to determine the daily variation. The urine Vitamin C** in these cases as well as in an additional thirty-nine cases was similarly analyzed. The same procedures were followed in a group of sixteen normal individuals. The results are shown in Table I and Table II.

TABLE I

Ascorbic acid in the blood of ulcer cases and normals

	No. of Cases	No. of Estimations	Range of Values in mg. %	Average in mg. %	Less Than 1 mg. %
Ulcer	27	86	0.30—1.44	0.63	20
Normal	16	20	0.58—1.38	1.44	3

From Tables I and II, it will be seen that there was a considerable overlapping of the results; the average level of Vitamin C in the blood and urine of ulcer patients was appreciably less than that of normal individuals. In patients on whom the blood and urine levels were followed from day to day, fluctuations amounting to 100 per cent were found. Furthermore,

TABLE II

Ascorbic acid in the urine of ulcer cases and normals

	No. of Cases	No. of Estimations	Range of Values in mg. %	Average in mg. %	Less Than 2.50 mg. %
Ulcer	66	290	0.10—5.10	1.20	46
Normal	30	51	1.30—9.20	4.05	6

the variations in the amount of ascorbic acid in the urine did not necessarily parallel that of the blood in the same patient, nor could these variations be accounted for by the diet.

The fact that the patients with peptic ulcer were confined to bed while the normal group were engaged in their usual activities may be an influencing factor in the results found. In order to gain more information concerning this point, similar procedures were

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**First morning urine

followed in a study of the urine levels of ascorbic acid in exophthalmic goiter cases, and in patients receiving bed treatment for functional disease of the digestive tract. The diet of both these groups was considered adequate in Vitamin C. The results are shown in Table III.

TABLE III

Ascorbic acid in the urine of cases of exophthalmic goiter and functional digestive diseases

	No. of Cases	No. of Estimations	Range of Values in mg. %	Average in mg. %	Less Than 2.50 mg. %
Exophthalmic Goiter	25	25	0.35—9.84	2.60	16
Functional	9	23	0.50—7.20	2.10	21

From Table III it will be seen that the Vitamin C excretion in these groups of patients who were confined to bed was similarly subnormal. The decreased levels of ascorbic acid in the urine of exophthalmic goiter patients has been noted by others.

It is our opinion that the above results cannot be considered as conclusive evidence that an actual Vitamin C deficiency was present in the cases of peptic ulcer studied (Tables I and II). Since it is believed that patients having an actual deficiency of Vitamin C require relatively larger amounts of ascorbic acid before evidence of the Vitamin is found in the urine, we attempted to test the response of ulcer patients to the daily administration of Vitamin C by following the excretion of ascorbic acid from day to day. Preliminary work revealed that appreciable amounts of ascorbic acid appeared in the morning urine in all cases when 400 mg. of Vitamin C* was given intravenously the previous night. Lesser amounts of Vitamin C produced no rise in ascorbic acid in the morning urine of most cases of peptic ulcer although normal individuals showed an appreciable effect from the administration of 300 mg. Accordingly, 300 mg. was given intravenously each night and the first morning specimen of urine analyzed for ascorbic acid in an additional group of cases. The results are shown in Table IV.

TABLE IV

Ascorbic acid in the a.m. urine of cases receiving 300 mg. of vitamin C intravenously each day at 10 p.m.—average values in mg. % for the groups are given

	No. of Cases	Days Followed:					
		0	1	2	3	4	5
Ulcer	11	1.97	6.17	8.87	21.4	29.4	39.9
Normal	2	4.20	91.0	162	—	—	—

As will be seen from Table IV, the normal individuals responded to the Vitamin C injections by excreting greater amounts of ascorbic acid than did the ulcer patients. In order to test the influence of the method of administration, the same dose (300 mg. of Vitamin C*) was given orally in a different group of patients and the urine excretion followed. An ad-

ditional group of patients confined to bed for functional digestive disorders was added to this series. The results are shown in Table V.

From the above tables it will be seen (Tables IV and V) that the intravenous administration of Vitamin C was more effective in increasing the amount of ascorbic acid in the urine of ulcer patients than was the same dose given by mouth. In normal individuals the method of administration did not appear to be a factor in the amount of vitamin excreted. Regardless of the method by which the Vitamin C was given, the response, as measured by the urine excretion of ascorbic acid, was greater in the functional disease group and normal group than in patients with peptic ulcer.

Since 300 mg. of Vitamin C given orally each night at 10 p.m. increased the morning urinary excretion of ascorbic acid (see Table V) the same dose was given in divided portions of 100 mg. throughout the day and the urinary excretion followed in an additional group of cases. The results of this series of cases are shown in Table VI.

As will be seen in Table VI, the general response to 300 mg. of Vitamin C given in divided doses was similar to that when the same amount was given in a single dose. The results as a whole lend credence to the view that the requirement of Vitamin C is greater in patients with peptic ulcer than individuals not so affected.

Since 100 mg. of Vitamin C given orally three times a day resulted in an excess excretion, it seemed reasonable to try smaller doses. Accordingly 50 mg. was given orally four times a day to an additional group of patients the results of which are shown in Table VII.

It would appear from the results of Table VII that 50 mg. of Vitamin C given orally four times a day furnishes an adequate amount for peptic ulcer patients whose requirements of Vitamin C are greater than those of normal individuals. Amounts greater than this are excreted in the urine.

DISCUSSION

Individuals showed wide fluctuations in their daily excretion of ascorbic acid, both patients with peptic ulcer and the controls. These fluctuations occurred in the group studied, who received no ascorbic acid, and

in the various groups on different doses. It was interesting to note the prompt fall from a high concentration to a subnormal value in any case in which the dose of ascorbic acid was withheld for one day. We were unable to account for these variations in excretion, as the diet, medication, and method of determination of ascorbic acid remained the same in all cases.

We believe that the extent of Vitamin C deficiency

*The Vitamin C used in this work was kindly supplied by Hoffman-La Roche, Inc.

in any one case cannot be ascertained from one urine analysis, but that the daily excretion levels must be studied for at least five days, and the response to dosage with ascorbic acid watched. (Other investigators (1) have been able to correlate the amount of Vitamin C in the diet over a period of months or

C results in an earlier and greater excretion of ascorbic acid in the urine in normal individuals, and patients on other dietary management, than in patients with peptic ulcer.

3. The amount of additional Vitamin C required to raise the excretion of ascorbic acid to normal in

TABLE V

Ascorbic acid in the a.m. urine of cases receiving 300 mg. of vitamin C orally each day at 10 p.m.—average values in mg. for the groups are given

	No. of Cases	Days Followed:								
		0	1	2	3	4	5	6	7	8
Ulcer	11	2.00	2.62	6.73	16.2	7.31	17.5	13.05	13.4	30.8
Functional	6	1.02	4.56	4.87	27.6	58.0	37.3	21.2	55.5	51.2
Normal	3	4.05	119	104	258	—	—	—	—	—

years, with the plasma ascorbic acid, apparently making only one determination in each case. Since the daily variation may be great, and since the plasma ascorbic acid does not necessarily parallel the urinary excretion level, we were unable to corroborate this work).

The administration of Vitamin C to the peptic ulcer patients did not alter in any evident manner the clinical course during hospitalization. They felt as well but apparently no better than patients on ulcer or other dietary management who did not receive Vitamin C. The free hydrochloric acid was not influenced by the ascorbic acid given. There appeared to be no difference as to the antacid used in the amount of ascorbic acid excreted, whether used singly, in combination, or if a change from one to the other was made. The length of time required to produce a significant rise of ascorbic acid in the urine could not be correlated with any factor in the course of the disease, the age, sex, diet or previous therapy. Patients with a history or presence of hemorrhage showed results indistinguishable from those without hemorrhage. Patients who had occult blood in the stool during the first few days of therapy could not be identified from others by the urine level of Vitamin C either before or during Vitamin C medication.

SUMMARY AND CONCLUSIONS

1. Evidence is presented to show that hospitalized patients on ulcer management have lower levels of ascorbic acid in the blood and urine than normal individuals or patients with functional digestive disorders.

2. Evidence suggesting that peptic ulcer patients require greater amount of ascorbic acid is demonstrated by the fact that daily medication of Vitamin

patients with peptic ulcer appears to be 50 mg. four times a day.

4. There appears to be no clinical evidence that ascorbic acid in doses large enough to maintain the excretion at the normal level is of any value in the treatment of patients with peptic ulcer with or without hemorrhage.

5. It is suggested that the metabolism of Vitamin C is influenced by activity and that lower blood and urine values are found in patients resting in bed than in active individuals.

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DISCUSSION

DR. SARA M. JORDAN (Boston, Mass.): Mr. Chairman: I am really not at all qualified to discuss this paper because I am not a biochemist. My only excuse is that it was done under the wing of the Gastro-Enterological Department at our clinic by Dr. Chamberlin, a member of the Department, and our research chemist, Mr. Perkin; however, there are a few facts which seem to me rather suggestive from both the experimental and the clinical point of view. The first was this day-to-day variation in the results which it seems to me must be very carefully taken into account when we talk about sub-clinical scurvy as an experimental condition.

Secondly, the fact that rest and activity seemed to play a part. That is perhaps a precocious conclusion, but at

TABLE VI

Ascorbic acid in the urine of cases receiving 100 mg. of vitamin C orally three times a day—average values in mg. for the groups are given

	No. of Cases	Days Followed:							
		0	1	2	3	4	5	6	7
Peptic Ulcer	3	1.60	2.10	2.35	2.75	3.17	10.6	23.2	28.8
Functional	3	2.10	3.16	4.52	6.97	31.7	24.9	24.0	29.0
Normal	6	4.05	6.70	13.2	37.4	13.6	61.8	37.1	—

least it is suggested by these data. The metabolic demands apparently are a factor in the findings of the cevitamic acid study.

Thirdly, it is interesting to note the fact that the presence of hemorrhage appeared to play no part in the variations which were found here.

Chamberlin's paper, 20 per cent of the people he classified as normal were low in C, and of his functional group, more than 20 per cent were low in C; in other words, it seems to me it is a difficult problem to combat functional or degenerative or infectious diseases unless we fuel the body properly.

TABLE VII

Ascorbic acid in the n.m. urine of cases receiving 50 mg. of vitamin C orally four times a day—average values in mg. for the groups are given

	No. of Cases	Days Followed:						
		0	1	2	3	4	5	6
Peptic Ulcer	7	1.56	1.60	1.51	3.23	2.51	6.75	5.20
Functional	3	1.00	1.76	1.41	2.44	3.88	9.00	6.75
Normal	4	3.38	8.92	22.4	25.9	16.8	15.7	—

From the clinical point of view it was suggested that excessive vitamin therapy was certainly useless. It was also suggested by the findings that vitamin therapy, bringing the cevitamic acid to normal, was a desirable thing. Whether or not it has any effect on the healing of the ulcer, we who used to give the low vitamin diets perhaps may doubt, because we certainly felt that in the days when we are now sure we did not have enough Vitamin C in the diet, the ulcer healing did take place.

In this matter it would be of interest to ask Dr. Brown, who was good enough to bring with him a slide showing the vitamin content of various diets, from the Mayo Clinic, to show the slide and discuss the paper.

Finally, one little point which I think is of interest, and that is the fact that during this study Dr. Chamberlin and Mr. Perkin checked the vitamin content of hot orange juice. It is our custom to give orange juice diluted with hot water, because we feel it is better tolerated by the ulcer patient, and sometimes by other patients. Occasionally we hear the criticism that orange juice loses its vitamin qualities thereby. Dr. Chamberlin and Mr. Perkins checked that and found that the orange juice itself could be brought to the boiling point without losing its vitamin qualities and, secondly, it could be diluted with hot water and still retain all of its Vitamin C.

DR. PHILIP W. BROWN (Rochester, Minn.): I always smile at the individual who comes enlisting somewhere and didn't plan to talk or do anything else and, when he is asked to say something, has a whole pocketful of slides. (Laughter)

My excuse for this slide is that I was talking at the Mississippi State Meeting the week before last, on nutritional problems, and Miss Mary Foley, of the Dietetic School of Nursing, had prepared this slide for me as part of that talk. I am offering this slide not in any manner of means discussing the etiology or therapy of ulcer, of which I know nothing, but merely to emphasize a point which apparently has been thought of more by the farmer and by his stock breeder, perhaps, than by us.

I think in these sacred walls here we can talk about diets, but when we get outside the walls, there is no one word that gives us more pain than the discussion of diets by all people who come into the office. (Laughter)

(Slide) It is interesting to note on this slide the low levels of vitamins in these particular diets. The ulcer diet is particularly low in B and in C. I will leave the significance of that to you. The high vitamin diet was of particularly great disappointment because it is high only in A and D, and I am not sure that we need that much A and D.

As you follow along in the long variety of gastro-intestinal conditions which are not sprue, nor pellagra, nor ulcer, nor true ulcerative colitis, it is amazing how deficient most of these people live; as you will notice in Dr.

DR. EDWARD S. EMERY, Jr. (Boston, Mass.): I should like to say a few words about this because we have also been interested in this subject.

It is generally agreed by what may be called the experts in this line that the blood serum, or the blood plasma levels have no relationship to the degree of saturation, that is the amount of Vitamin C in the body we have also found this; for example, one patient which we studied required only 600 milligrams of ascorbic acid to become saturated, although his blood plasma level was 0.6; whereas another one whose blood plasma was 0.7, required 1500 milligrams of Vitamin C.

Secondly, it is also agreed that there is no relationship between the blood values and the spill in the urine. We had one patient, for example, whose blood value was 0.6, who spilled 20 milligrams without any added Vitamin C; and another, 1.36, who spilled none in the urine.

Dr. Ralle showed this morning that there is no threshold value for the blood level. Therefore, we used the method of Heineman and Van Eekelen, whereby they saturate their patients with Vitamin C, giving large doses by mouth until it spills over, and then wait ten days, saturate them again, and find how much it takes to produce another spill. By this means we found that the daily requirement of the peptic ulcer patient, appears to be a little higher than the normal. The normal requirements, as given by Van Eekelen and Heineman, are 0.85 milligrams per kilogram of body weight per day.

In the ulcer patients we have studied, it has varied from 0.91 to 1.2, with an average of 1.02. Therefore, this would suggest, that ulcer patients have a slightly higher requirement for Vitamin C, but it is of no importance because an extra orange each day will take care of the deficit.

DR. MARTIN G. VORHAUS (New York, N. Y.): A word of caution as we go into the discussion of the vitamins: It is well to recall that we are discussing a vitamin which is water soluble and probably not stored in the body. Unless we know a great deal about the previous diets of these ulcer patients, as we do in experimental animals, it is somewhat of an inaccuracy to speak of saturation of any water soluble vitamin.

Dr. Chamberlin pointed out that he studied these cases for eight days, and at the end of that time these patients were still not saturated. The degree of saturation has been stated in the terms of one unknown, i.e. How long was any given patient on a subminimal intake? But other unknowns have not been mentioned, namely—the amount of any vitamin necessary for any given patient, which is modified by the basal metabolism of the individual, infection, the amount of work and other factors. Unless we

know all the variables in patients we cannot draw adequate conclusions as to their individual vitamin requirement.

DR. DONALD T. CHAMBERLIN (Boston, Mass., closing the discussion): I wish to thank the discussers. First I should like to speak about the point of saturation. There must be some other factor besides simple saturation, since 200 milligrams given per day give a significant rise

on the same diet that 300 milligrams do. There is much yet to be learned about the metabolism of Vitamin C and I believe until we know how the normal behaves, all the results so far in any group of patients with any disease are not significant. Until we know whether an active individual on his feet, with an adequate diet, has the same Vitamin C blood and urine levels after he has been in bed, on that same diet, we cannot be sure that these results mean anything.

Vagotomy Plus Partial Gastrectomy for Duodenal Ulcer*

By

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WHILE the cause of peptic ulcer is still unknown, there is today a strong tendency to regard the disease as a nervous affection. There is a mass of accumulated evidence that it is caused in most cases by a psychogenic disturbance. The nervous pathway presumably is the vegetative nervous system chiefly the vagus which acts by producing increased motor and secretory activities leading eventually to the ulcer disease.

Whatever the ultimate cause of ulcer may be, all observers seem to agree that the acid factor is of central importance. On several occasions we have presented our studies on the acid factor before the Association. We demonstrated, using an orange test meal, that the nervous phase of gastric secretion was very high in duodenal ulcer and that the chemical phase was low to normal both in gastric and duodenal ulcer. We also demonstrated that the harmful nocturnal acid secretion was greatly increased in peptic ulcer. According to Babkin, this is also a vagally conditioned phenomenon. Because of these observations and the fact that peptic ulcer, either primary ulcer or post-operative recurrent ulcer, does not in our experience occur in an achlorhydric stomach, we advocated milk drip to continuously neutralize the day and night secretion medically and partial gastrectomy to produce a harmless achlorhydria without recurrence surgically. As a result of many years of experience with both methods we recommend them strongly in the therapy of peptic ulcer.

It is our purpose today to present the important problem of recurrences after partial gastrectomy. It has been our experience that partial gastrectomy invariably produces a true achlorhydria without recurrences in patients with gastric ulcer on the lesser curvature. In duodenal (or juxtapiyloric) ulcer on the other hand, it produces an apparent achlorhydria only in 50% of the cases despite extensive resection. It is in the group with retained acid that we have encountered recurrent jejunal ulcers. In order to avoid reoperation for peptic ulcer an apparent or true achlorhydria is the ideal state. We have not seen a recurrent ulcer when there is a post-operative achlorhydria. It is probable that the most important factors in the

question of the post-operative acidity are the following: (1) The removal of the antrum (abolishes the chemical phase) (2) the amount of fundus secretory tissue removed (extent of resection) (3) the duodenal regurgitation (4) the vagus nerve irritability and (5) the amount of gastritis present. The first three factors are physiologic and the last two are pathologic. Therefore, the fact that subphrenic vagotomy plus partial gastrectomy in dogs may not produce an achlorhydria in a Pavlov pouch should not be an argument against such a procedure in the human where the additional pathologic processes mentioned above come into play.

It is our chief purpose here to demonstrate the acidity in peptic ulcer patients before and after partial gastrectomy with particular reference to the problem of preventing post-operative recurrences in the patients with duodenal ulcer with a high pre-operative acidity.

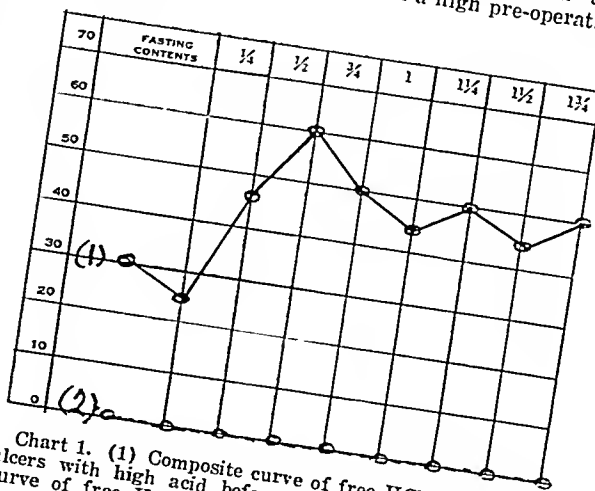


Chart 1. (1) Composite curve of free HCl in 10 gastric ulcers with high acid before operation. (2) Composite curve of free HCl in the same 10 gastric ulcers after partial gastrectomy without vagotomy. (3 weeks).

Note: In all gastric ulcers at the angle irrespective as to whether the acid is high before operation as in this curve or low, there is practically always an immediate and late true achlorhydria. (This results from the removal of the antrum, high resection, inhibition by gastritis or from the intestine).

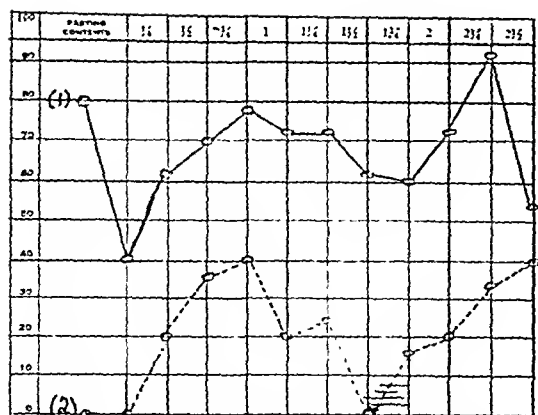


Chart 2. (1) Composite curve of free HCl in 38 duodenal ulcers before operation. (2) Composite curve of free HCl in the same 38 duodenal ulcers, 3 weeks after partial gastrectomy (without vagotomy).

Note: Partial gastrectomy alone in duodenal ulcers with high pre-operative free HCl produced an immediate post-operative achlorhydria only in 3 cases. (Persistence of vagal hyperirritability with retained secretory tissue).

Briefly our studies have demonstrated the following:

1. Patients with gastric ulcer who have either a high or a low preoperative free HCl practically invariably have an achlorhydria without recurrences post-operatively. (Chart I)

2. Patients with duodenal (or juxtapiyloric) ulcer with a high pre-operative acidity (over 60—chiefly 70-100) rarely get an achlorhydria (immediate or late) after partial gastrectomy. (Charts II and III)

3. Patients with duodenal (or juxtapiyloric ulcer) with a normal free HCl (20-40) pre-operatively in a large per cent of the cases develop a post-operative achlorhydria without recurrences. Chart IV)



Chart 3. (1) Composite curve of free HCl in 24 cases of duodenal ulcer with a very high pre-operative acidity. (2) Composite curve of free HCl in the same 24 cases after partial gastrectomy without vagotomy. All the cases in this group had repeated fractional test meals from 1½ to 4 years post-operatively. Only 1 patient in this group developed an achlorhydria 9 months after operation. 4 other patients had an immediate post-operative achlorhydria.

Note: In the entire group of duodenal ulcers, 59 cases, all with very high pre-operative acidity, only 8 (13%) developed a post-operative achlorhydria. Apparently partial gastrectomy alone in patients with a high free pre-operative acidity produces achlorhydria in duodenal ulcers only in a small per cent of cases.



Chart 4. (1) Composite curve of free HCl in 23 duodenal ulcers before operation with low acidity (20-40 free HCl). (2) Composite curve of free HCl in 7 of these cases (trace of free HCl persists). (After partial gastrectomy without vagotomy). (3) Composite curve of free HCl in 16 of these cases—all 16 developed an immediate achlorhydria which persisted. (After partial gastrectomy without vagotomy).

Note: In 23 cases of duodenal ulcer with a low normal free HCl (20-40) 16 or 70%, developed an immediate achlorhydria. Apparently partial gastrectomy alone will produce an achlorhydria in most duodenal ulcers with a low preoperative acidity.

4. Patients with a high pre-operative acidity in duodenal ulcer form the group in which post-operative recurrent jejunal ulcer occurs. (Chart V)

5. Subphrenic anterior vagotomy plus partial gastrectomy produces an achlorhydria (immediately or later) in most duodenal ulcer patients with a very high pre-operative acidity. (Charts VI and VII)

6. It is probable but not proved that the addition of this procedure, viz; anterior vagotomy, may prevent almost entirely post-operative recurrences in duodenal ulcer.

7. Because of the fact that gastro-enterostomy heals duodenal ulcer but favors the production of jejunal ulcer (probably by the effect of the increased gastric motor and secretory activities on the jejunum) gastro-enterostomy plus subphrenic vagotomy has been advocated and used in the treatment of a small, selected group of duodenal ulcers.

8. Finally, a renewed, careful study of the technique, indications, and results of subphrenic anterior or anterior plus posterior vagotomy alone or in combination with other surgical procedures in the therapy of peptic ulcer seems highly desirable.

DISCUSSION

DR. IRVIN ABELL (Louisville, Ky.): I really feel incompetent to discuss the material presented by the essayist since we have had no personal experience with vagotomy and but a comparatively limited one with massive resection in duodenal ulcer. With your indulgence I will present our reasons for what may be regarded on the part of the essayist as ultraconservatism in our clinic. We regard peptic ulcer as primarily a medical problem, assuming surgical significance only with its complications, sequelae and intractable chronicity. These are perforations, repeated bleeding and obstruction due to cicatrization. A single massive hemorrhage is not regarded as an indication for operation: a chance for healing under medical treatment should be afforded until further bleeding or chronicity demonstrates its futility. Chronicity in spite of appropriate treatment is accepted as a failure of the latter and an indication for operation. Since duodenal ulcers do not show a tendency to malignant degeneration, it has been argued that chronicity alone does not justify resort to operation. The danger of perforation, the menace of hemorrhage, the possibility of obstruction and the continued discomfort produced by the chronic ulcer, which

proves resistant to an intelligently planned medical treatment, afford sufficient grounds in our opinion to negate this assumption. The discussion this afternoon has confirmed our belief that the cause of duodenal ulcer remains submerged in obscurity, and furthermore that achlorhydria is not a sine qua non for healing. With these postulates

CHART V

Recurrent jejunal ulcers after partial gastrectomy without vagotomy

Name	Pre-operative Free HCl	Post-operative	Complication
Wyche	75	20	Jejunal ulcer, perforated. Ceased
Strongen	77	40	Jejunal ulcer with hemorrhage
Wevix	95	42	Jejunal ulcer, penetrating
Eisenberg	62	48	Jejunal ulcer, penetrating
Chose	60	78	Jejunal ulcer. Ceased
Clarín	60	88	Jejunal ulcer, penetrating
Berger	78	80	Jejunal ulcer, hemorrhage
Friedman	100	80	Jejunal ulcer, hemorrhage
Plotaky	130	52	Jejunal ulcer, hemorrhage
Beer	64	50	Jejunal ulcer, penetrating
Coopersmith	90	110	Jejunal ulcer, penetrating
Guarneri	24	30	Jejunal ulcer, penetrating
Zeis	75	73	Jejunal ulcer, penetrating

Note: In 13 cases with jejunal ulcer after partial gastrectomy for duodenal ulcer, all but one case had a high pre-operative free acidity. Is it possible that the addition of high, anterior subphrenic vagotomy in this group would have prevented or lessened the occurrence of jejunal ulcer by producing an achlorhydria?

established in our belief we have employed the more conservative operations, selecting for each individual case the one best suited for the correction of the pathology it presents. When the ulcer is situated on the anterior wall of the duodenum and the parts can be satisfactorily mobilized, excision of the ulcer with a modified pyloroplasty gives a mortality rate of approximately one per cent and a freedom from symptoms in approximately ninety per cent. When location of ulcer or fixation of the parts do not lend themselves to this procedure, destruction of the ulcer with the cautery combined with a posterior gastro-enterostomy will give approximately the same results as to mortality and relief of symptoms. With marked obstruction a posterior gastro-enterostomy may be done with reasonable safety and with reasonable assurance of relief. These conservative procedures will meet the indications in the majority of simple duodenal ulcers and the results obtained place the burden of proof upon advocates of other methods to show just cause for such advocacy. When the ulcers are multiple, and they are in from five to six per cent: when situated on the posterior wall, difficult of access and so calloused as to render healing difficult: and when so situated the ulcer has perforated into the head of the pancreas with fixation of the duodenum and pylorus to the latter organ, we have come to the resection of the duodenum and pylorus. The extent of the resection in such instances is determined by the local pathology, either a Billroth I or II as local conditions permit. We have not employed massive resections with the avowed intention of

producing achlorhydria, since this condition is neither essential for the healing of ulcer nor necessary in the prevention of recurrence: furthermore, permanent achlorhydria disrupts the physiology of digestion, the ultimate effects of which while still undetermined may conceivably be distressing. Since we have had this experience, namely, a low operative mortality and a high percentage of relief, we feel that conservative surgical procedures plus intelligent supervision on the part of the gastro-enterologist or internist, offer a method of treatment preferable to the more radical application of surgery in the treatment of duodenal ulcer.

DR. JULIUS FRIEDENWALD (Baltimore, Md.): Dr. Winkelstein and Dr. Berg have presented an important paper.

If hyperchlorhydria plays as important role in the etiology of ulcer as many of us maintain and as it is certainly largely involved in the prevention of its healing, any measures by means of which hyperacidity can be overcome and achylia brought about should be employed in order to effect complete healing.

It is interesting to learn from the work of Drs. Winkelstein and Berg that this can be accomplished by means of vagotomy in association with other surgical procedures.

In a series of experiments on dogs reported some years

CHART VI

Partial gastrectomy with anterior vagotomy for duodenal ulcer followed by achlorhydria

Name	Pre-operative Free HCl	Post-operative		
		Immediate	Late	Follow-up
Kohn	74	30	2 yrs. 14—3 yrs. 0	6 yrs. well
Sussman	116	0		5 yrs. well
Destler	70	30	1 yr. 0	4½ yrs. well
Asseo	90	40	1 yr. 0—4 yrs. 0	4 yrs. well
Frelch	100	0	6 mos. 0	2 yrs. well
Richardson	80	0	1 yr. 0—4 yrs. 0	6 yrs. well
Gluck	100	20	4 yrs. 0	5½ yrs. well
Goodman	100	0	2 yrs. 0	4 yrs. well
Kaplan	110	20	4 mos. 0	6 yrs. well
Kanofsky	96	46	10 mos. 0—1 yr. 0	6 yrs. well
Krellan	90	0	8 mos. 0	7 yrs. well
Bader	76	20	6 mos. 20—2 yrs. 0	6 yrs. well
Haggett	62	0	4 mos. 0	7 yrs. well
Levine	80	0	2 yrs. 0	8 yrs. well
Meyer	90	0	2 yrs. 0	9½ yrs. well
Pavell	90	0	1½ " 0	9 yrs. well
Greenberg	62	22	4 mos. 0—5 yrs. 0	6 yrs. well
Rosen	74	0		3 mos. well
Podol	90	0	7 mos. 0—7 yrs. 0	8 yrs. well
Ehrenberg	94	20	7 mos. 0—4 yrs. 0	7 yrs. well
Fichter	58	0		4 yrs. well
Coopersmith	110	0		5 yrs. well
Hyman	80	0	2 mos. 0	2 mos. well
Baxter	94	12	1 yr. 0	9½ yrs. well
Bucholtz	106	0	1 yr. 0	2½ yrs. well
N. Cohen	90	4	2 yrs. 0	

Note: 26 cases of Duodenal Ulcer with very high pre-operative acidity. 16 developed an achlorhydria immediately and the other 10 developed an achlorhydria in 4 months to 3 years. All 26 cases followed for 4 to 9 years and in all cases were well. The vagotomy is apparently harmless.

ago by Dr. Feldman and myself, the observation was made that by means of vagotomy alone changes in the gastric secretion due to section of the vagus were inconstant and that there was likewise a general tendency for the secretion to return to normal after a time when diminished as the result of this operation.

CHART VII

Partial gastrectomy with anterior vagotomy for duodenal ulcer followed by persistent free acid

Name	Pre-operative Free HCl	Post-operative Free HCl		Follow-up
		Immediate	Late	
Wollinsky	83	30	1 yr. 30 2 yrs. 30	8 yrs. well
Hodes	95	20	6 mos. 22	5 yrs. well
Milner	74	20	7 mos. 10	6 yrs. well
Lillenberg	90	20	4 mos. 30	5 yrs. well
Kurchick	135	36	1 yr. 22	5 yrs. well

Partial gastrectomy with anterior vagotomy for duodenal ulcer followed by persistent free acid (no follow-up)

Name	Pre-operative HCl	Post-operative HCl
Gilman	104	16
Morosi	104	30
Zawitz	75	50
In 5 cases followed up, the acid persisted but there were no recurrences. In 3 cases acid persisted (there was no follow-up)		
Summary:		
Total number of cases		34
(Immediate)		16
(Later)		10
Persistent Acid (for 4 months to 2 years)		5
Persistent Acid (no follow-up)		3

Conclusion: In duodenal ulcers with high pre-operative acidity, partial gastrectomy alone results in achlorhydria only in a small per cent of the cases (13%). In duodenal ulcers with high pre-operative acidity partial gastrectomy plus anterior subphrenic vagotomy is followed by achlorhydria in a high per cent of the cases (77%).

Similar results were obtained from subphrenic vagotomy as well as from section of other portions of the nerve. Due to this uncertainty it is possible that the very favorable results obtained by Drs. Winkelstein and Berg are due to the combined effect of the gastric operation and vagotomy.

DR. ALBERT J. SULLIVAN (New Haven, Conn.): A view was expressed earlier this afternoon that acid isn't the only factor in the production of ulcer and I submit that we are already approaching a point where we can begin to formulate a theory as to the mechanism behind the ulcer problem. We have the observations of Harvey Cushing that the hypothalamic lesions produce gastric ulcerations. We have studies of those interested in the personality of patients with ulcer, their driving dynamic personality which keeps them on the go all the time; that plays a role in the ulcer mechanism, and the report of Dr. Necheles last year, physiological experiments stressing the point that acetylcholine as liberated by the parasympathetic nervous system by stimulation of the vagus, may be the chemical mechanism of the production of peptic ulcer, and today we have further evidence given by Dr. Winkelstein that this vagus factor is important.

It is a very complicated mechanism; it isn't neurogenic,

purely neurogenic, or purely psychogenic, or purely the chemistry of the autonomic nervous system, but a combination of all three; and I wish to mention a very unusual case which I have had the opportunity of seeing, a patient with myotonia congenita, a disease resulting in a stiffness of the muscles caused by an excess of acetylcholine and that can be relieved by giving the patient quinine, which prevents the action of acetylcholine on the cells.

This patient had an intractable duodenal ulcer. His myotonia was relieved by quinine and so were his ulcer symptoms.

Purely on a theoretical basis I am using quinine in a small group of selected cases in an attempt to prevent ulcer recurrences. It is too early to even report on the results.

We have also used atropin to neutralize the chemical effect of vagus stimulation through a different mechanism, and I believe all we need are a few more facts to bridge the gaps between all these theories and we can soon have a complete, logical exposition for the mechanism of peptic ulcer.

DR. BORIS P. BABKIN (Montreal, Canada): I should like to discuss this paper from a physiological point of view. I must confess that to me such operations as, e.g., a subtotal gastrectomy or section of vagi does not look at all physiological. However, the aim of Dr. Winkelstein and Dr. Berg's operation was to diminish the gastric acidity, and it seems that the only sure surgical way to do it was that adopted by them. The justification for the anterior vagotomy is that at the cardia the anterior or left vagus is a mixed nerve, which contains fibres from the left and right cervical vagi. The mixing of the vagal fibres occurs above the diaphragm. Therefore the section of the left or anterior vagus branches at the cardia will diminish to a certain extent the secretion in all parts of the stomach.

I should like to ask Dr. Winkelstein how he explains that an ulcer reappears more often after the operation for duodenal ulcer than after the operation for gastric ulcer. I understand that during the operation for gastric ulcer a much greater part of the stomach is removed than during the operation for duodenal ulcer. However this does not seem to explain everything. La Barre (Bruxelles) showed, e.g. that the secretory function of the fundus, or "poch à air" as the French are calling it, is in normal conditions under a lesser vagal control than the same function of the corpus of the stomach. However, under certain circumstances the relations may change. This was demonstrated by La Barre in a following way. One dog has a gastric pouch formed from the fundus (poch à air), another possessed a pouch formed from the corpus. The gastric secretion was activated by means of insulin which stimulates the vagal centre in the brain. The corpus pouch responded to administration of insulin by a copious secretion already on the second day after the operation. The fundus pouch, on the other hand, required from two to three months to acquire the ability to secrete gastric juice under the influence of insulin. Since not so much organ is resected in the case of duodenal ulcer, than in the case of gastric ulcer, the secretory function of the vagus is, in the first case, very little affected by this operation or is more quickly restored than in the second case. But the possibility of the restoration of the vagal secretory function must be kept in mind.

DR. ASHER WINKELSTEIN (New York, N. Y., closing the discussion): I am indebted to the discussers for their interesting observations.

With reference to Dr. Abell's statement that achlorhydria may not be the sine qua non for the healing of ulcer, we feel definitely from a very long experience with a large series of surgical cases that it is definitely the sine qua non for the prevention of ulcer recurrences. In our

experience we have yet to see a true recurrent ulcer in the jejunum after a partial gastrectomy which is followed by a false or true achlorhydria.

Our experience with gastro-entrostomy is unfavorable. We found a high percentage of recurrences. We believe at present that partial gastrectomy is the operation of choice for gastric and duodenal ulcer. We believe that subsequent work may prove that certain cases of duodenal ulcer may be subjected to gastro-enterostomy plus subphrenic vagotomy.

With reference to a question as to the harmful effects of postoperative achlorhydria, we have a large series of patients followed up for fifteen years who had an achlorhydria after partial gastrectomy. Many of these had a true achlorhydria, they have not shown any anemia or other harmful effects from the achlorhydria.

Professor Babkin has asked me to explain why it is that we get achlorhydria and no recurrences after gastric ulcer, whereas we get acid and recurrences after duodenal ulcer in some cases. We have found in gastric ulcer that the pre-operative acidity is quite low. Post-operatively there is invariably an achlorhydria. It is true achlorhydria

as proved by histamine and neutral red. Since it is a true achlorhydria, there are two possibilities; one that the secretory tissue is almost completely excised, and the other a gastritis is present which inhibits the glands. It is possible that the two together are responsible for the achlorhydria.

In gastric ulcer where the lesion is at the lesser curvature angle a larger resection is forced on the operator than in duodenal ulcer.

The final point, made by Dr. Sullivan, seems to concern itself with the question of terminology. We believe one should differentiate sharply between the ultimate cause of peptic ulcer and the mechanism by which it is produced. At present I think the ultimate cause is one of three possibilities, psychogenic disease, ductless gland disease, and possibly an inflammatory disease, gastritis or duodenitis, leading to ulcer. Concerning the mechanism, I believe all observers will agree with me in saying that three factors are of vital importance there, viz; the irritant, the acid and the tissue susceptibility factor. The second, or acid factor, seems of central importance in the ulcer problem.

The Development and Healing of Gastric Ulcer—A Clinical, Gastroscopic, and Roentgenologic Study

By

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and

FREDERIC E. TEMPLETON, M.D.

THE essence of the ulcer problem is to be found in two closely related processes: the pathogenesis of the lesion and the mechanism of healing. For the past several years we have been engaged in a careful study of gastric ulcer, focussing our attention upon these two aspects. It is apparent that the only objective methods available for the protracted observation of ulcer are those of roentgenology and gastroscopy. Frequent use of both of these methods has been made in the patients under observation.

A year ago a preliminary report (1) was published in which it was pointed out that X-ray and gastroscopy are complementary rather than competitive methods of examination. We have frequently noted that small ulcers, visible gastroscopically, may not be seen by X-ray and, on the other hand, that ulcers identified roentgenologically may not be found gastroscopically. In this latter group the lesions usually occur in the so-called gastroscopic "blind areas," particularly along the lesser curvature of the antrum and on the posterior wall of the body of the stomach near the lesser curvature. The importance of checking gastroscopically a negative X-ray examination, or vice versa, is comparable to that of checking the fluoroscopic examination with films.

A careful study of the appended case reports will reveal the extent of these discrepancies and will also show that occasionally the same ulcer may be seen at one gastroscopic or roentgenologic examination and not be seen at another time even with the same method, although the lesion is known to be still present.

This article is based primarily upon fourteen cases, chosen to illustrate certain definite points. A brief summary of these cases and protocols of the gastroscopic and roentgenologic examinations in each are given. The important points to be brought out are: (1) that an acute ulcer may appear and disappear quickly; (2) that an ulcer may increase in size; (3) that after complete healing has taken place an ulcer may recur in approximately the same location or in an adjacent area; (4) that symptoms may be entirely absent; (5) that the mucosal changes may vary from a perfectly normal mucosa to superficial, atrophic, or hypertrophic gastritis, with or without hemorrhages or pigment spots; (6) that the rate of healing varies greatly in different cases; (7) that adequate nutrition, acid neutralization, and avoidance of concurrent infection are important in promoting healing; and (8) that those cases exhibiting delayed healing are often accompanied by interference with gastric emptying and usually with narrowing of the antrum.

PATHOGENESIS

Theories of ulcer formation have been generally divided into the chemical, infarctive, traumatic, and inflammatory (2). Günstzberg (3) in 1852 related gastric ulcer to the effect of the gastric juice on the mucous membrane. Subsequently Rokitsansky (4) and R. Virchow (5) postulated the concept of organic or functional closure of the vessel with resultant hemorrhagic or anemic necrosis and digestion of the necrotic tissue by the gastric juice. These views were supported by Hauser (6), von Bergmann (7), and many others, and have been the prevailing theories of ulcer

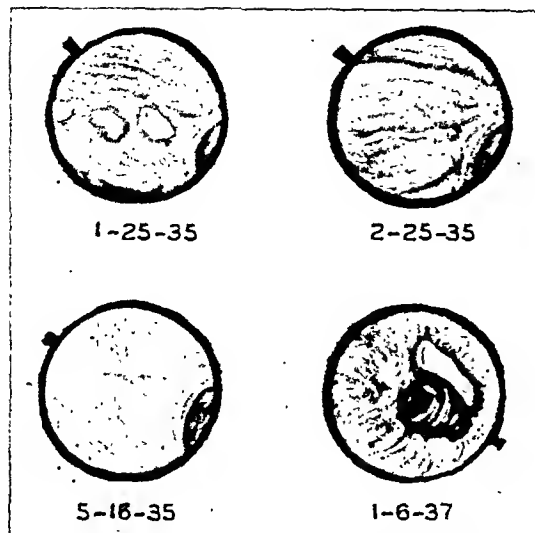


Fig. 1 (Case 1). Three of the six ulcers found on January 25, 1935, are well shown. Note their complete disappearance by February 25. The large ulcer adjacent to the gastro-enterostomy stoma, found January 6, 1937, was found in a control examination, produced no symptoms, and subsequently was found to have healed completely.

formation. There is evidence that abnormal trauma may play a role in the development of ulcer but there is every reason to think that this is a rare occurrence. The fourth theory, namely the inflammatory basis of

ulcer, has in recent years been most ardently supported by Moszkowicz (8), Konjetzny, Puhl (9) and others. The evidence offered is chiefly pathologic. This point of view is well stated by Konjetzny in the following paragraph:

"Es ist gleich ein Streitpunkt vorwegzunehmen, der sich darauf bezieht, ob die drei Formen der geschwürigen Bildung im Magen und Duodenum (Erosion, akutes und chronisches Ulcus) ineinander übergehen oder ob das typische Ulcus von vornherein in seiner Form vorausbestimmt ist, wie es vor werden: *das typische Ulcus des Magens und des Duodenum entsteht aus einer Erosion, der erste Vorgang der Geschwürsbildung spielt sich also in der Schleimhaut ab*" (10)."

It is important to point out that this concept resembles the chemical theory in that it postulates a progressive penetrating process.

There is abundant experimental evidence that the ulcer process begins in the mucosa and penetrates into the submucosa, and muscularis. The clinical behavior of peptic ulcer is, of course, in accord with this view for it is well recognized that a chronic ulcer may undergo massive hemorrhage or acute perforation—a process presumably due to extension and penetration of the lesion. Relatively few direct, objective, clinical observations have been reported to substantiate this assumption. Berg (11) has published two roentgenograms of a gastric ulcer taken at an interval of one and a half years definitely showing an increase in size. Ten days after the last examination the ulcer perforated. Buckstein (12) refers to the "gradual increase in the size of a gastric niche coincidental with aggravation of the clinical symptoms. Forssell (13)

*Italian ours.

CASE 1

H. M., Female, Age 33, Unit No. 120421, X-ray No. 37762

The patient had had gnawing epigastric distress from 1928 to 1930 when a posterior gastro-enterostomy was performed. Distress recurred in 1934. The patient entered the hospital January 21, 1935, and was discharged symptom-free February 27, 1935. During 1936 there was no definite distress even at the time of the gastroscopic demonstration of ulcer in November, 1936, and January, 1937. The distress recurred in July, 1937, but no studies were made (patient did not report). Maximum free acidity (control aspiration) 32. The roentgenologic and gastroscopic data follow:

X-RAY		GASTROSCOPY		
			Ulcer	Mucosa
1-25-35	Two gastric ulcers just above the angle, opposite the gastro-enterostomy stoma; upper one, 3 mm. wide, 2 mm. deep; lower one, 8 mm. wide, 5 mm. deep.	1-25-35	Six shallow ulcers along lesser curvature, four in a line and two on the anterior wall. The uppermost ulcer was the largest, appearing to be about 4 cm. long.	Edge of ulcers hyperemic, mucosa otherwise normal; gastro-enterostomy with pylorus-like activity.
2-25-35	No ulcer seen.	2-25-35	Ulcers healed.	One small hemorrhagic erosion in anterior wall; large pigment spot, lesser curvature; slight superficial gastritis high on lesser curvature and about the gastro-enterostomy stoma.
		5-10-35	No ulcer.	Two small mucosal hemorrhages, lesser curvature.
		7-18-35	No ulcer.	Normal.
		3-25-36	No ulcer.	Two pigment spots beneath cardia.
		11-11-36	Two shallow ulcers between stoma and pylorus.	Normal.
1-6-37	Stoma ulcer?	1-6-37	Large marginal ulcer in the gastric mucosa adjacent to the gastro-enterostomy stoma.	Mucosal hemorrhages of lesser curvature—one hemorrhagic erosion of lesser curvature.
		4-28-37	No ulcer seen.	Chronic hypertrophic gastritis of lesser curvature above the angulus.
4-28-37	No ulcer.			

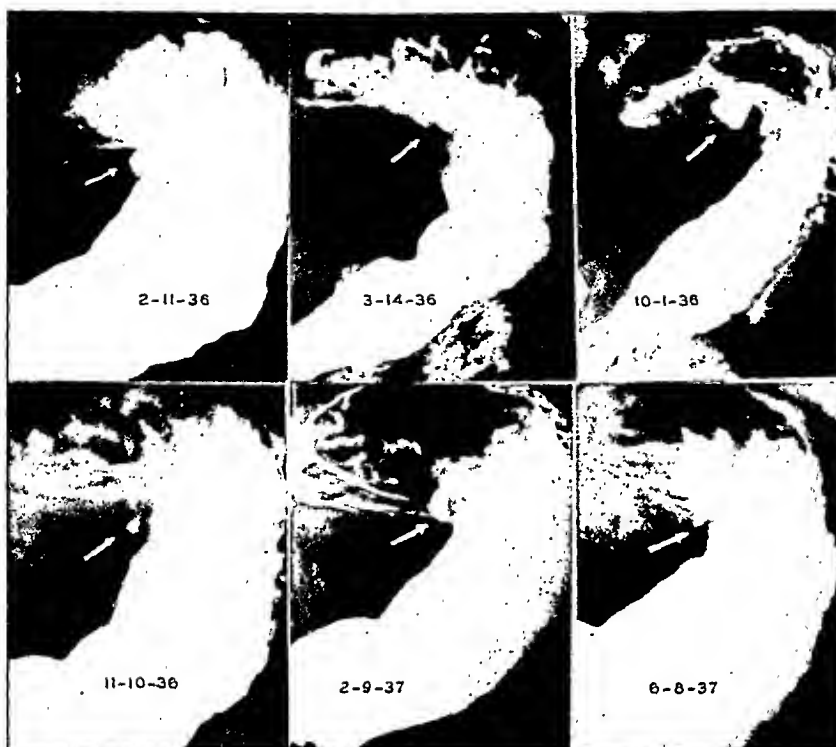


Fig. 2 (Case 3). Note the definite variation in the size of the lesion from time to time.

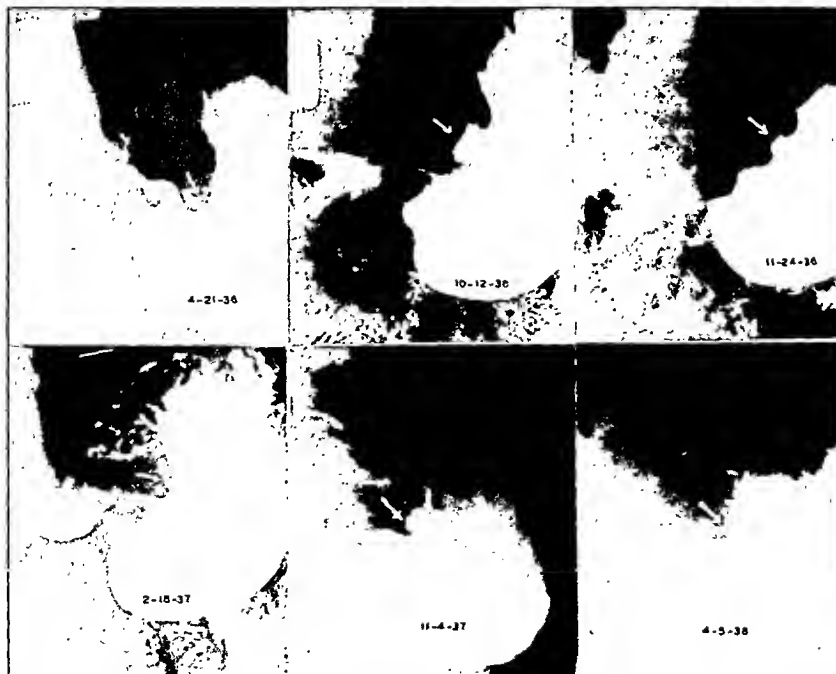


Fig. 3 (Case 4). Note the definite increase in the size of the lesion between April 26 and October 12 and its subsequent decrease in size to November 24 and February 18, the increase apparent November 4 and the decrease again by April 5, 1938. The narrow antrum is evident in all of the views.

implies such a process in the clause, "If the disease process wins the upper hand and necrosis and infiltration proceed*..." Cole's conception (14), on the other hand, is that "the pathogenesis of ulcer is similar to that of a boil. The ulcer begins as an area of inflammation within the wall of the gut, and as this goes on

CASE 2

L. H., Female, Age 24, Unit No. 123238, X-ray No. 38626

The patient entered the hospital March 18, 1935, because of an epigastric "pressure sensation" of one year's duration, intermittent, relieved by vomiting. She was discharged symptom-free March 30, 1935, on "Sippy" management. April 11th she was readmitted because of the passage of a tarry stool. The stools soon became negative for occult blood on ulcer management and the patient was discharged May 13, 1935. Indefinite abdominal distress has continued to date (December 22, 1937), not of the ulcer type, and induced apparently by fatigue and emotional disturbances. Maximum free acidity (Ewald) 34. The roentgenologic and gastroscopic data follow:

X-RAY		GASTROSCOPY		
			Ulcer	Mucosa
3-5-35	No ulcer	3-8-35	Red bleeding shallow ulcer, upper lesser curvature.	Normal.
3-20-35	No ulcer	3-23-35	No ulcer seen.	Hypertrophic gastritis at the site of the ulcer.
4-26-35	No ulcer	4-24-35	Marked gray-yellow ulcer in the area of hypertrophic gastritis.	
		5-10-35	Shallow ulcer.	No gastritis.
		7-16-35	No ulcer.	No gastritis; small hemorrhages in the mucosa in the fornix.
		3-24-36	No ulcer.	No gastritis; streak-like hemorrhage in region of old ulcer.

to liquefaction necrosis, it breaks into the lumen of the gut, and then the necrotic core is extruded into the lumen or it may also simultaneously break into the peritoneum." Extension of a lesion once formed is not compatible with this concept.

Gutzeit and Teitge (15) have well described the breakdown of an "Ulcusrezidiv" with recurrent ulcer formation as observed gastroscopically:

"Jede Ulcushheilung passiert dieses Stadium der ungenügend gefestigten Narbe. Hierbei sind die Ulcusränder zwar schon zusammengezogen. Zwischen ihnen aber befindet sich ein feiner Spalt, aus dem ein heller Fibrinstreifen hervorsieht. In dieser Phase sind die Beschwerden meist abgeklungen, und röntgenologisch ist eine Nische nicht mehr darstellbar. Das Ulcus scheint also nach dem klinischen und röntgenologischen Befund geheilt zu sein. Bei der gastroscopischen Kontrolle wird erst der verhängnisvolle Irrtum solcher Annahme aufgezeigt. Das Ulcusrezidiv des ungeheilten Ulcus kann nur bei rechtzeitiger Kenntnis des

oberflächenanatomischen Befundes verhütet werden. Denn gestattet man einem solchen Kranken eine Lockerung seiner diätetischen Lebensweise, dann brechen die eben verklebten Ulcusränder wieder auseinander, und der offene Geschwürskrater tritt wieder zutage,* ein Ereignis, das eine mehrwöchige Ulcusbehandlung um ihre Früchte zu bringen vermag. Nicht

CASE 3

R. M., Female, Age 56, Unit No. 145262, X-ray No. 45939

The patient entered the hospital February 7, 1936, because of periodic epigastric distress of three years' duration. She was discharged on ulcer management February 20, 1936, but she did not follow the program carefully. Distress recurred in August, the crater recurred, and the patient was readmitted October 22, 1936. The pain disappeared, the crater decreased in size, and the patient was discharged November 11, 1936. In January, 1937, the pain recurred and the crater had enlarged. The patient was instructed to remain in bed at home on strict Sippy management for one month and was finally induced to continue the strict program for a year. Neither the pain nor the ulcer has reappeared. Maximum free acidity (histamine) 100. Gastroscopy was not performed (resistance at the cardia), but the roentgenologic findings are tabulated:

X-RAY		GASTROSCOPY	
		Ulcer	Mucosa
2-11-36	Gastric ulcer beneath cardia, 12 mm. wide, 6 mm. deep.	(Gastroscopy not performed because of resistance at the cardia).	
3-14-36	Scar, but no crater (pain gone).		
10-1-36	Crater in same place, 19 mm. wide, 13 mm. deep (recurrent distress).		
11-10-36	6 mm. wide, 5 mm. deep (pain gone).		
2-9-37	15 mm. wide, 9 mm. deep (recurrent pain).		
3-9-37	No ulcer (pain gone).		
6-8-37	No ulcer (pain gone).		
8-10-37	No ulcer (pain gone).		
10-19-37	No ulcer (pain gone).		
12-28-37	No ulcer (pain gone).		
3-31-38	No ulcer (pain gone).		

eine Lockerung, sondern eine gewissenhafte Weiterführung der diätetischen Behandlung kann solchen Schaden wirksam verhüten."

The sudden appearance of an acute ulcer and its subsequent rapid healing has been noted rather frequently in our studies. An excellent illustration is that of Case 1 (Fig. 1) in which six discrete ulcers along the lesser curvature were observed gastroscopically on January 25, 1935. A month later they had disappeared, leaving no trace behind. A similar process occurred in Case 2, the protocol only being given. These small ulcers were scarcely visible roentgenologically.

Definite evidence has been obtained in several of the cases under observation that small ulcers may increase in size (Cases 3 to 11 inclusive). In Case 3,

*Italics ours.

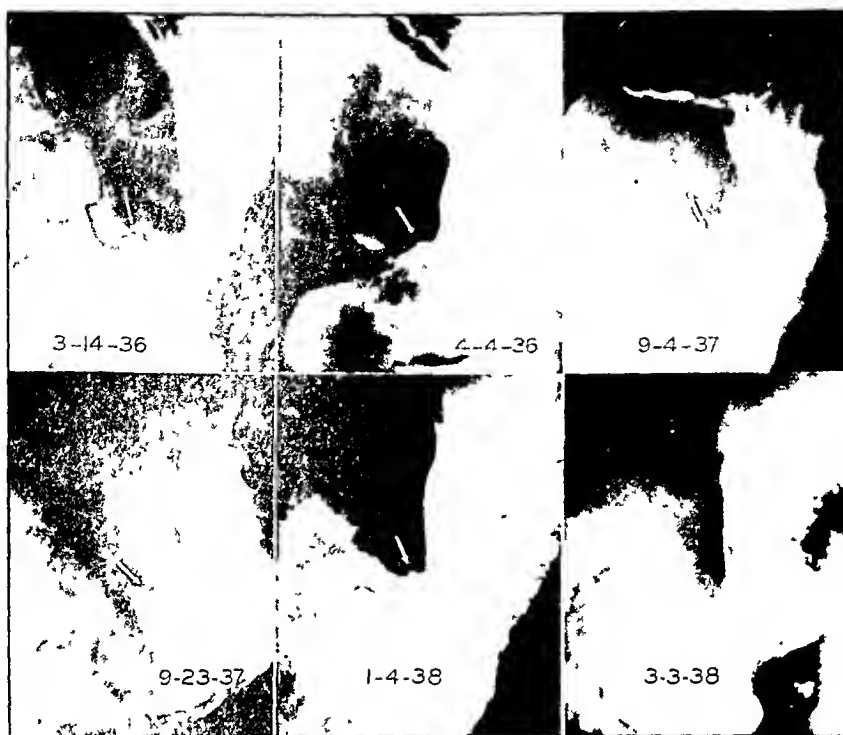


Fig. 4 (Case 5). The variation in the size of the ulcer is apparent. The constant narrowing of the antrum is well shown in four of the six views.

roentgenologic evidence only is available but this is definite as may be seen from Fig. 2. In Case 4, the most definite evidence of increase in size is the roentgenologic in which the marked progression of the lesion is unmistakable if one compares the initial film, taken 4-21-36, with the later one, taken 10-12-36, Fig. 3. In Case 5, the variations in size observed roentgenologically may be easily seen in Fig. 4. Similar changes were seen gastroscopically. In Case 6, the variations are clearly shown roentgenologically in Fig. 5 but are perhaps more difficult to follow in the protocol of the gastroscopic examinations. It is significant in this connection that estimation of the size of the lesion is more difficult gastroscopically than it is roentgenologically. In Case 7, the protocol shows clearly the changes in the size of the lesion as observed both roentgenologically and gastroscopically. In Case 8, the X-ray examinations were definite but the gastroscopic evidence was even more conclusive, Fig. 6. In this instance the localization of the lesion was facilitated and made more exact gastroscopically by the constant finding at the site of the ulcer of an unusual pattern of the rugae. The decrease in the size of the ulcer from April 4 to April 14 and its reappearance at the same site by September 1 is unmistakable. In Fig. 7, the X-ray evidence of similar alterations in the prepyloric ulcer of Case 9 is clear. Case 10 is quite similar, the lesion decreasing from November 19, 1934, to February 16, 1935, increasing by December 14, disappearing by April 4, 1936, and continuing absent in October, 1936, and February, 1938, during which time the patient remained well clinically, Fig. 8. The ulcers in these two cases

were in a gastroscopic "blind area" but nevertheless in the second, Case 10, the lesion was visible in three of the five gastroscopic examinations made. In Case 11, the recurrent lesion, repeatedly seen roentgenologically in April, May, June and September of 1937, increased in size in October and November (Fig. 9). It is interesting to note that this definite ulcer was not seen gastroscopically until November when it was described as "gigantic." Fig. 10 is included to show a splendid illustration of the same process in a duodenal ulcer (Protocol not given). The progressive enlargement of the crater is unmistakable in the first four views and its subsequent decrease in the following views is equally clear.

In this series the extension of the lesion usually occurred without any symptoms. This is probably due to the fact that the patients were on a more or less modified Sippy program, the modification being inversely proportional to the willingness and ability of the patient to carry out the program. Generally speaking, and with certain exceptions to be noted later, the greater the modification, the greater was the likelihood of increase rather than decrease in the size of the lesion or of recurrence if the ulcer had healed.

In Case 12, the complete healing of the ulcer was shown by repeated roentgenologic and gastroscopic examinations. The ulcer reappeared at the same site, just above the angulus, six months later but apparently healed promptly. Eight months later another lesion appeared slightly lower on the lesser curvature (Fig. 11). This lesion was just below the angulus whereas the two previous lesions were just above it.

Fig. 12 shows the disappearance of the first ulcer located on the angulus and the subsequent formation of a new ulcer in the antrum as seen gastroscopically. In this instance we have to do, then, with recurrence at a definitely different site.

The protocols of Cases 13 and 14 illustrate healing and recurrence at approximately the same site. These observations are quite in accord with the following statement made by Schindler (16) in 1937: "Frequently the new ulcer occurs in exactly the same place as the original lesion; sometimes it is in immediate proximity to the original site, and sometimes in a different place." The observations are also consistent with the known tendency of ulcers to recur after gastroenterostomy. A similar phenomenon is observed in the occasional development of gastric ulcer in patients known previously to have had duodenal ulcer.

It is noteworthy that acute ulcers often were not accompanied by symptoms as for instance in Case 1, in which the acute ulcers seen gastroscopically in November, 1936, and January, 1937, were accidental findings only. Similarly increase in size was frequently noted

without distress or other symptomatic evidence of progression. (See Cases 6 and 11 particularly). It seems to us clear that this clinical evidence is in complete accord with the view that ulcer formation is the result of an "erosive" rather than infarctive process and that chronic ulcer develops from an acute ulcer. The cause of the initial erosion is not touched upon here. Erosions are roentgenologically invisible. Gastroscopic evidence of the relationship between erosions and ulcer is perhaps a matter of definition. Both Schindler and Gutzeit agree, however, that an ulcer may develop from the so-called "ulcusrezidiv."

This question leads at once to a consideration of the relationship between ulcer and the so-called mucosal changes, or, more specifically, gastritis. Pathologically, Konjetzny finds gastritis constantly present in ulcer, the gastritis being of the so-called "antral" type, involving particularly the lesser curvature of the stomach, the antrum, and the first portion of the duodenum (Puhl (9)). Gastroscopically the mucosal changes in our cases varied greatly. In some the mucosa was normal; in others hemorrhages, pigment

CASE 4

A. M., Male, Age 75, Unit No. 149893, X-ray No. 47526

The patient entered the hospital April 20, 1936, because of occasional attacks of vomiting of five years' duration. There had been no pain. A gastric ulcer was demonstrated roentgenologically. Further hospitalization for treatment was advised and refused. On October 10, 1936, the patient was readmitted because of massive, almost fatal, hematemesis and melena. The patient was discharged symptom-free December 11, 1936, but the ulcer has not completely healed to date (April 5, 1938). Deep radiation therapy was administered for ten days in daily doses of approximately 300 r (measured in air), alternately through anterior and posterior portals directed at the upper two-thirds of the stomach, the total dosage being 2930 r, the last treatment being given October 13, 1937. Maximum free acidity (histamine) 58. The roentgenologic and gastroscopic data follow:

X-RAY		GASTROSCOPY	
		Ulcer	Mucosa
4-21-36	Ulcer just above the incisura angularis, 6 mm. wide, 3 mm. deep. Pyloric narrowing; 24-hour retention.		
10-12-36	Ulcer in same region, 25 mm. wide, 12 mm. deep.		
11-24-36	15 mm. dia., 16 mm. deep.		
12-29-36	10 mm. dia., 7 mm. deep.	12-10-36 Healing ulcer on angulus.	Two small mucosal hemorrhages.
1-20-37	7 mm. dia., 4 mm. deep.	1-20-37 Large benign ulcer above angulus.	One hemorrhagic erosion of posterior wall in mid-part of body.
2-18-37	5 mm. dia., 4 mm. deep.	2-24-37 Ulcer much smaller; converging folds.	Hypertrophic gastritis about the ulcer.
3-18-37	8 mm. dia., 12 mm. deep.	3-24-37 Ulcer crater invisible; converging folds at the angulus.	Nodular hypertrophic gastritis of greater curvature of antrum and of posterior wall.
5-23-37	3 mm. dia., 2 mm. deep.		
6-23-37	No ulcer seen.		
8-20-37	No ulcer seen.		
9-27-37	3 mm. dia., 3 mm. deep.	9-29-37 Spasm; ulcer area not visible.	
11-4-37	10 mm. dia., 5 mm. deep.		
		12-1-37 Ulcer at angulus.	Atrophic gastritis of antrum and superficial gastritis of body.
12-25-37	3 mm. dia., 2 mm. deep.	1-6-38 No ulcer seen.	Slight superficial gastritis of antrum and body.
2-10-38	3 mm. dia., 2 mm. deep.	2-16-38 Remnant of former ulcer, 1 to 2 mm.	
		3-16-38 No ulcer seen.	Chronic superficial gastritis.
4-5-38	2 mm. dia., 1 mm. deep.		

Narrowing of the smooth and pliable antrum was constantly noted throughout each examination but the narrowing has become less marked in the more recent examinations.

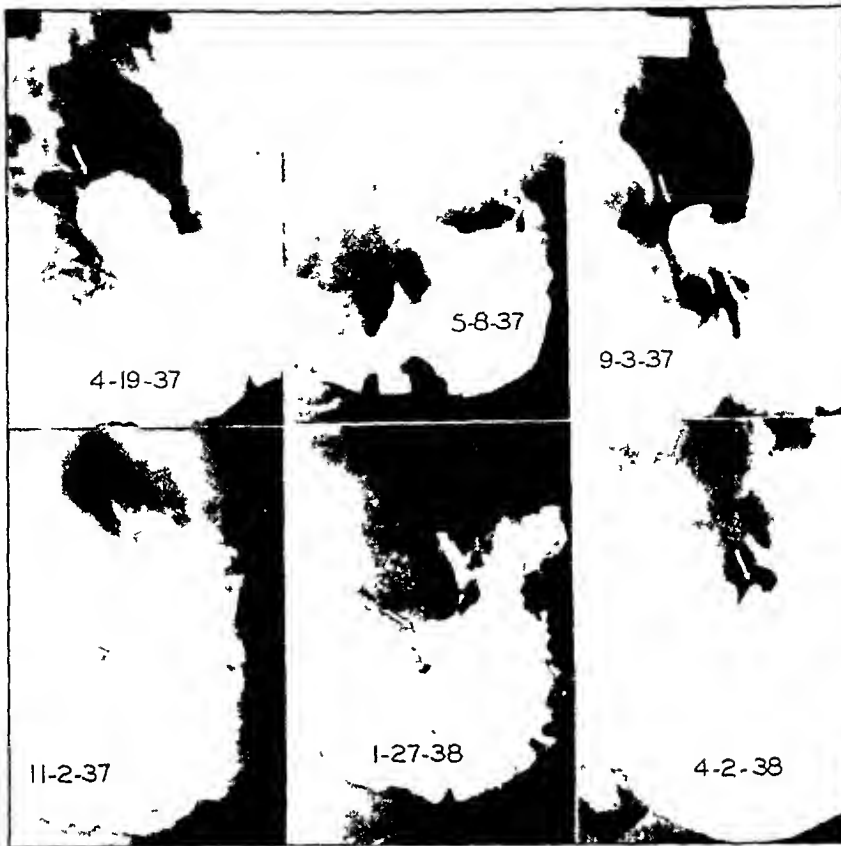


Fig. 5 (Case 6). Note the decrease in the size of the crater from April 19 to May 8, the subsequent increase by September 3, the decrease again to November 2, the definite enlargement again by January 27, and once more the decrease to April 2.

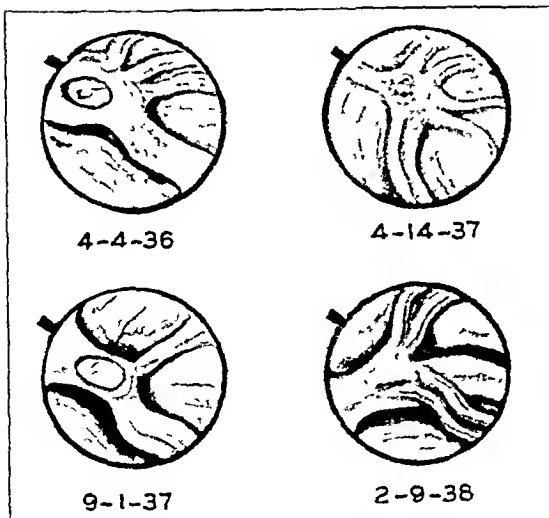


Fig. 6 (Case 8). Note the definite decrease in the size of the ulcer from April 4, 1936, to April 14, 1936, the ease of localization by means of the characteristic pattern of the folds, the increase in the size of the ulcer from April 14, 1937, to September 1, 1937, and subsequent healing by February 9, 1938. The mucosa is essentially normal.

spots, and hemorrhagic erosions were seen; superficial gastritis was not infrequent and hypertrophic gastritis of all grades of severity was a common finding. Not only did the changes vary greatly from patient to patient but also in the same patient from time to time, as may be noted by examining the protocols. In Case 7, for instance, the mucosal change varied from a marked hypertrophic gastritis to normal mucosa with one pigment spot and numerous small hemorrhagic areas, to a hypertrophic gastritis, then to a normal mucosa, then a hypertrophic gastritis in varying grades of severity and, most recently, a chronic superficial gastritis.

HEALING PROCESS

Roentgenologically, it has been known for years that even though the niche of a penetrating gastric ulcer is quite large, it may disappear quickly under treatment. This does not prove that the healing is complete for the ulcer may persist after the niche has disappeared. Schindler, however, observed gastroscopically the disappearance of an ulcer and epithelization in five and one-half weeks. He has subsequently observed lesions in which the healing process was much more delayed. Rapid healing has already been mentioned as having been seen in several of our patients, particularly Cases 1, 2, 12, 13 and 14. In several, however, healing has been very, very slow. Thus, in Case 6, Fig. 5, it is not complete at the end of a year,

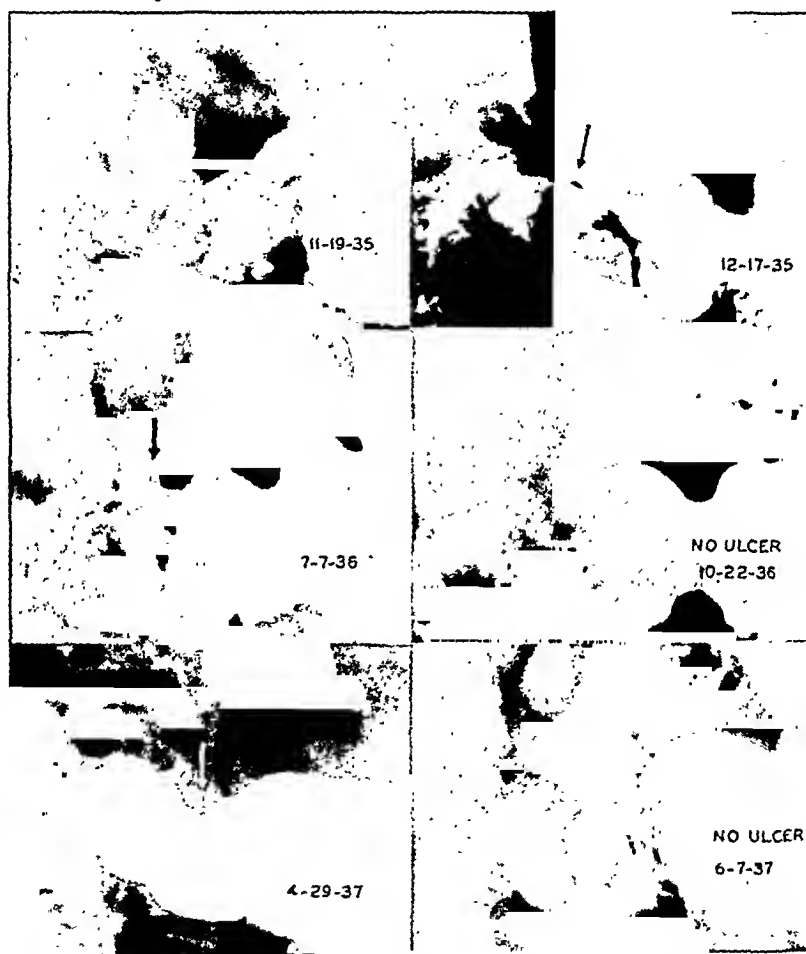


Fig. 7 (Case 9). Note definite variation in size of prepyloric ulcer in the first three views, its disappearance in the fourth, and its recurrence in the fifth.

and in Cases 4 and 5, Fig. 3 and 4, it is not yet complete at the end of two years. In studying the various cases in an attempt to discover the cause of the slow healing or of the recurrences, there seems to be reason to attribute the difficulty in many instances to the failure of the patient to carry out the program of rest, high-calorie diet, and acid neutralization. This was specifically true in Cases 3, 7, 8, 9 and 10. When sufficiently impressed with the importance of the regime or when hospitalized, all of these patients would make excellent progress symptomatically and the ulcer would improve objectively. Complete healing apparently occurred in Cases 3, 9 and 10, when they finally became adequately impressed with the necessity for continuous, vigorous treatment and, in Case 8, when it was made economically possible for the patient to follow the program. Concurrent infection did not seem to play a *specific* role in either recurrence or exacerbation but, on the other hand, it was frequently observed to have a deleterious effect in the same manner as overwork, worry, fatigue, and the failure to follow the prescribed regimen.

In several cases, however, healing occurred very

slowly even though the management was faithfully followed (Cases 4, 5, 6 and 7). It is noteworthy that in all of these gastric emptying was slow and that, except in Case 6, the antrum of the stomach was persistently narrow although pliable and smooth as in Figs. 3 and 4. This narrowing of the antrum has been known for many years, having been described by Carmen (17) and attributed to reflex spasm. Golden (18) has recently called attention to this condition again and suggests that it is due to an "inflammatory reaction of the gastric wall. . . It seems possible that the mechanism of the antral spasm is an effect of edema and inflammation on the ganglions." The subject was discussed in detail by Schindler and Templeton (19) last year. In the series of cases under consideration the gastroscopic examination did not disclose a satisfactory explanation of the narrowing of the antrum. No more evidence of gastritis was found, on the whole, in the group with antral narrowing than in the group without this condition. Gastroscopy, of course, visualizes only the mucosa and the finding of a normal mucosa does not disprove the possibility that inflammation may be present in the muscularis, as we have

CASE 5

T. L., Male, Age 54, Unit No. 147849, X-ray No. 46658

The patient gave an indefinite story of intermittent epigastric distress of at least two, and perhaps seven, years' duration. He entered the hospital March 12, 1936, and was discharged on treatment April 11, 1936. He did not follow the treatment carefully and in May, 1937, the distress recurred. The patient then resumed and fairly well maintained the prescribed program. Deep radiation therapy was administered for ten days in daily doses of approximately 300 r (measured in air), alternately through anterior and posterior portals directed at the upper two-thirds of the stomach, the total dosage being 2930 r, the last treatment being given September 18, 1937. Distress has not recurred to date (April 23, 1938). The ulcer has varied in size from time to time and is not yet healed. Maximum free acidity (histamine) 130. The roentgenologic and gastroscopic findings are tabulated:

X-RAY		GASTROSCOPY		
			Ulcer	Mucosa
3-14-36	Gastric ulcer at angle, 10 mm. wide, 15 mm. deep; radiating mucosal folds, duodenal deformity, no crater.			
3-20-36	9 mm. wide, 7 mm. deep	3-18-36	Benign crater-like ulcer in the angulus.	Pallor of mucosa—no gastritis.
4-4-36	5 mm. wide, 2 mm. deep.	4-2-36	Healing benign ulcer at angulus.	No gastritis; large fresh hemorrhage high on posterior wall, bleeding into cavity of stomach.
4-10-36	4 mm. wide, 1.5 mm. deep.	4-17-36	Healing gastric ulcer at angulus, shaped like a five-pointed star.	Marked superficial gastritis, lesser curvature.
5-27-37	Ulcer, 8 mm. wide.			
5-23-37	5 mm. wide.	6-23-37	Normal stomach.	
9-4-37	3 mm. wide, 2 mm. deep.	9-1-37	No ulcer.	Hypertrophic gastritis, antrum and posterior wall.
9-23-37	8 mm. wide, 4 mm. deep.	9-21-37	Healing ulcer at angle.	Slight superficial gastritis—two mucosal hemorrhages.
10-5-37	9 mm. wide, 7 mm. deep.			
11-3-37	Shallow ulcer.			
12-6-37	4 mm. wide, 2 mm. deep			
1-4-38	13 mm. wide, 2 mm. deep.	2-9-38	Ulcer 15 mm. wide.	Superficial gastritis.
3-3-38	Ulcer gone.			
3-30-38	Shallow ulcer seen at the angle, 3 mm. wide, 2 mm. deep.	3-30-38	Two benign ulcers of the lesser curvature of the angulus and the antrum.	No inflammation.

In each and every roentgenologic examination the antrum was described as narrow but pliable.

indeed observed pathologically in one case. It seems unlikely that spasm of the antrum would be as constant and persistent as the antral narrowing observed in these cases has been. Hypertrophy of the pyloric muscle, as described by many workers since Cruveilhier (20), may also have been present and may have been the sole cause of the delayed emptying in Case 6 (Fig. 5). Differentiation is difficult clinically between hypertrophy of the pyloric muscle, spasm of the muscle, and failure of the muscle to relax, the so-called achalasia of the pylorus (Hurst (21)). Regard-

less of the mechanism involved, gastric retention was definitely present in this group of cases and, in our opinion, played a very significant role in retarding the healing of the ulcer.

CONCLUSIONS

1. The clinical, gastrosopic, and roentgenologic evidence support the concept of ulcer as a penetrative process beginning in the mucosa and invading the deeper layers of the gastric wall.
2. The healing process, under favorable conditions,

CASE 6

W. F., Male, Age 59, Unit No. 173277, X-ray No. 56016

The patient entered the hospital April 18, 1937, because of epigastric pain of the ulcer type of only five and a half months' duration. It had been accompanied by anorexia, weakness, vomiting, constipation, and a thirty-five-pound loss of weight. On ulcer management the pain subsided promptly, the stools became free of occult blood, the patient gained weight, and the ulcer decreased in size. The patient was discharged May 26, 1937, and seen frequently in the out-patient department. Deep radiation therapy was administered for nine days in daily doses of approximately 300 r (measured in air), alternately through anterior and posterior portals directed at the upper two-thirds of the stomach, the total dosage being 2651 r, the last treatment being given August 9, 1937. He continued to feel well but because of objective evidence of increase in the size of the ulcer, he was readmitted to the hospital September 1, 1937. The ulcer again decreased in size, and so the patient was discharged October 6, 1937. He continued in excellent health and strength but the lesion increased in size upon his return to work. He was therefore readmitted January 29, 1938, and has remained in the hospital to date (April 25, 1938). The lesion is decreasing slowly in size. Occult blood is consistently absent from the stool. The patient looks and feels well and is gaining in weight (total gain to date, 7.4 kg.). Maximum free acidity (histamine) 60. The roentgenologic and gastrosopic data are shown in the following summary:

X-RAY			GASTROSCOPY	
			Ulcer	Mucosa
4-18-37	Ulcer of lesser curvature 4 cm wide.	4-25-37	Benign ulcer.	Atrophic hemorrhagic gastritis of fundus (unusual in benign ulcer).
5-8-37	16 mm. wide.	5-12-37	Ulcer smaller, radiating folds.	
		5-19-37	Ulcer 50% smaller than last time; converging folds.	Chronic superficial gastritis about ulcer.
5-23-37	15 mm. wide.	6-2-37	Healing ulcer.	Chronic hypertrophic gastritis about ulcer.
6-20-37	17 mm. wide.	July, 1937	Healing chronic benign ulcer with five radiating folds.	Normal.
		8-11-37	Healing ulcer, shallower.	Normal.
9-3-37	23 mm. wide.	9-1-37	Ulcer; elevation in floor—food retention or carcinoma?	On greater curvature opposite.
		9-10-37	Ulcer, benign—elevation seen in last examination apparently food.	Normal.
9-21-37	20 mm. wide.	9-24-37	Ulcer shallower but at least 2 or 3 cm. wide; four converging folds.	Normal.
10-5-37	18 mm. wide.	10-1-37	Ulcer shallower—small red polyp-like protuberance in sharp anterior edge—carcinoma?	Normal.
		10-11-37	Ulcer healing, protuberance present.	Normal.
10-15-37	13 mm. wide.	10-20-37	Ulcer healing, shallower—edges irregular from ingrowing islands of mucosa.	One hemorrhage.
11-2-37	13 mm. wide.			
12-21-37	16 mm. wide.	12-16-37	Large shallow ulcer, not crater-like but very irregular; former islands of mucosa gone.	Normal.
1-27-38	17 mm. wide.	1-29-38	Ulcer about 1.5 cm. wide.	Swollen mucosa about ulcer.
2-12-38	15 mm. wide.	2-11-38	Healing ulcer.	Surrounding gastritis.
		2-18-38	Large, shallow, irregular ulcer with ragged edges surrounded by reddened halo.	Inflammation about ulcer.
3-12-38	16 mm. wide.	3-7-38	Ulcer now seen beyond the rugae; ulcer seemed to be divided into two portions by a ridge of mucosa.	Mucosa of angle swollen and thickened, that of entire stomach reddened and mottled—due to food retention?
4-2-38	9 mm. wide.	3-31-38	Ulcer deeper and more regular than at last examination.	Slight inflammation about ulcer.
4-21-38	9 mm. wide.			

Delayed gastric emptying was present throughout as evidenced by the fluid retention noted at the beginning of each examination and, in the later examinations particularly, by the difficulty in getting the barium to leave the stomach. There was no narrowing of the antrum. The pylorus appeared to be in spasm, or at least it failed to open.

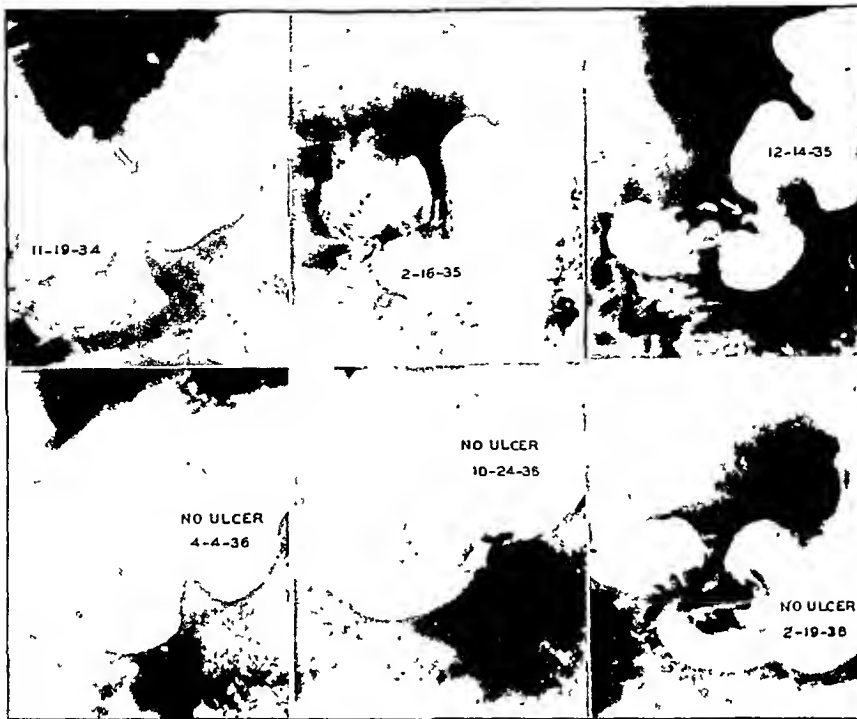


Fig. 8 (Case 10). Note the decrease in size from November 19, 1934, to February 16, 1935, the increase by December 14, and the disappearance by April 4, 1936. The lesion did not recur subsequently judging from the examinations of October 24, 1936, and February 19, 1938, and the continued lack of symptoms.

proceeds rapidly and leads to "restitutio ad integrum" so complete that the scar is scarcely visible gastroscopically.

3. Failure of the lesion to heal may be due to the failure or inability of the patient to carry out an adequate regimen of rest, acid neutralization, and diet, or to failure of the stomach to empty properly.

4. Delayed gastric emptying in gastric ulcer is frequently associated with and probably attributable to organic or physiologic narrowing of the antrum, failure of the pylorus to open, or both. The mechanism involved is not yet entirely clear.

Note (Sept. 20, 1938): The patient, W. F. of Case 6, was submitted to operation by Dr. Alexander Brunschwig on June 25, 1938. A hypertrophy of the pylorus was found, accounting presumably for the continued gastric retention. The lesser curvature of the stomach was adherent to the left lobe of the liver by a fibrotic cord. A partial gastrectomy was performed, three-fifths of the stomach being removed. A small ulcer, measuring about 5 mm. in diameter, was found in the mucosa near the site of the adhesion of the lesser curvature to the liver. Convalescence has been uneventful. The gastric ulcer of Case 11, patient W. R., recurred again in June, symptoms having been present for one month. Healing is not yet complete, as evidenced by repeated gastroscopic and roentgenologic observations.

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DISCUSSION

DR. MARTIN E. REHFUSS (Philadelphia, Pa.): Mr. Chairman, Ladies and Gentlemen: I don't believe I have ever seen or heard a much better paper. I am very much impressed not only with the pictures but also with the

excellent X-ray findings that are so beautifully visualized that no one could possibly miss them.

When Dr. Boles asked me to discuss this paper, it took me back to the question of the diagnosis of gastric ulcer. I have always maintained that the only diagnosis that counted was the visual diagnosis by X-ray or by gastro-scope. It was my good fortune to spend six months with Dr. Haudeck, in Vienna, a little over twenty-six years ago,

and he was making the diagnosis of gastric ulcer by noticing the first material that enters the stomach (using blackboard). I can well recall as the material went down the stomach, Dr. Haudeck would point out the necessity for examination with the first few mouthfuls of opaque material in such fashion you would see the little tack-like crater.

A little later on when we became very much more

CASE 7
W. G., Male, Age 46, Unit No. 144032, X-ray No. 45433

The patient gave a history of periodic epigastric pain of fourteen years' duration. "Ulcer" was said to have been found by X-ray in 1922 and again in 1928. Under ambulatory management the patient became symptom-free and the ulcer healed. A "modified Sippy" program was continued, but the pain and the crater recurred in March and April, 1937. The pain subsided promptly upon the resumption of a more strict program, but the crater diminished slowly, as seen in the table to follow. Deep radiation therapy was administered for ten days in daily doses of approximately 300 r (measured in air), alternately through anterior and posterior portals directed at the upper two-thirds of the stomach, the total dosage being 2930 r, the last treatment being given September 22, 1937. Maximum free acidity (histamine) 115. The roentgenologic and gastroscopic data follow:

X-RAY		GASTROSCOPY		
			Ulcer	Mucosa
1-10-36	Gastric ulcer just above angle; 7 mm. wide, 5 mm. deep; irregular antrum — gastritis?	1-20-36	Ulcer at angulus; curious pouch formation at anterior margin of angulus — perigastric adhesion?	Marked hypertrophic gastritis of the body, not of the antrum.
		2-14-36	Ulcer smaller; pouch the same.	Gastritis improved.
3-11-36	3 mm. wide, 1 mm. deep; irregular antrum, retained fluid.	3-14-36	Ulcer decreased to about one-fourth its previous size.	Marked gastritis still present.
		4-18-36	Ulcer almost healed; pouch unchanged.	Hypertrophic gastritis still present.
		6-16-36	Ulcer at angulus 5 mm. in diameter.	No significant gastritis; one pigment spot and numerous small mucosal hemorrhages.
7-2-36	5 mm. wide, 2 mm. deep; antral narrowing.	7-22-36	Very small ulcer; 3 mm. in diameter; same pouching.	Hypertrophic gastritis of body.
8-12-36	No ulcer.	8-12-36	Scar; 3 converging folds.	Mucosa normal.
4-13-37	Ulcer just above the incisura angularis; 3 mm. wide, 4 mm. deep.	4-14-37	Round, not very deep ulcer just above the angulus, 5 to 6 mm. in diameter.	Hypertrophic gastritis of anterior wall just above the angulus.
5-11-37	4 mm. wide, 2 mm. deep.	5-12-37	Narrow antrum; ulcer almost healed.	Chronic hypertrophic gastritis of anterior wall, high on lesser curvature.
5-25-37	3 mm. wide, 2 mm. deep.	6-2-37	No ulcer.	Severe hypertrophic gastritis of lesser curvature and antrum.
6-4-37	4 mm. wide 3 mm. deep.			
6-24-37	No ulcer			
6-3-37	5 mm. wide, 4 mm. deep.	9-6-37	Recurrent ulcer with surrounding inflammation.	Slight inflammatory reaction about ulcer.
9-24-37	5 mm. wide, 2 mm. deep.	9-24-37	Ulcer definitely larger.	Improving chronic hypertrophic gastritis.
10-10-37	7 mm. wide, 3 mm. deep.	10-15-37	Ulcer about the same size.	No hypertrophic gastritis; slight superficial gastritis.
		10-27-37	Ulcer unchanged.	Chronic hypertrophic gastritis about ulcer.
11-0-37	5 mm. wide, 4 mm. deep.	11-10-37	Ulcer smaller.	Superficial chronic gastritis of antrum and upper part of stomach.
11-27-37	3 mm. wide, 2 mm. deep.	11-24-37	Healing ulcer.	Slight superficial gastritis of upper part of stomach.
12-7-37	No definite ulcer seen.	12-6-37	Almost-healed ulcer.	Slight superficial gastritis of upper part of stomach.
12-24-37	3 mm. wide, 2 mm. deep.	12-11-37	Very tiny ulcer — 2 mm.	Slight superficial gastritis of upper part of stomach.
1-20-38	No ulcer	1-13-38	Healed ulcer of angle.	Slight superficial gastritis of upper part of stomach.
		2-2-38	No ulcer.	Marked superficial gastritis.
2-11-38	Esophageally, no ulcer seen. Film shows shallow ulcer, 3 mm. wide, 3 mm. deep.			

The roentgenologist (FET) described persistent narrowing of a stomach and pyloric antrum at every examination except the last one when it had apparently disappeared.

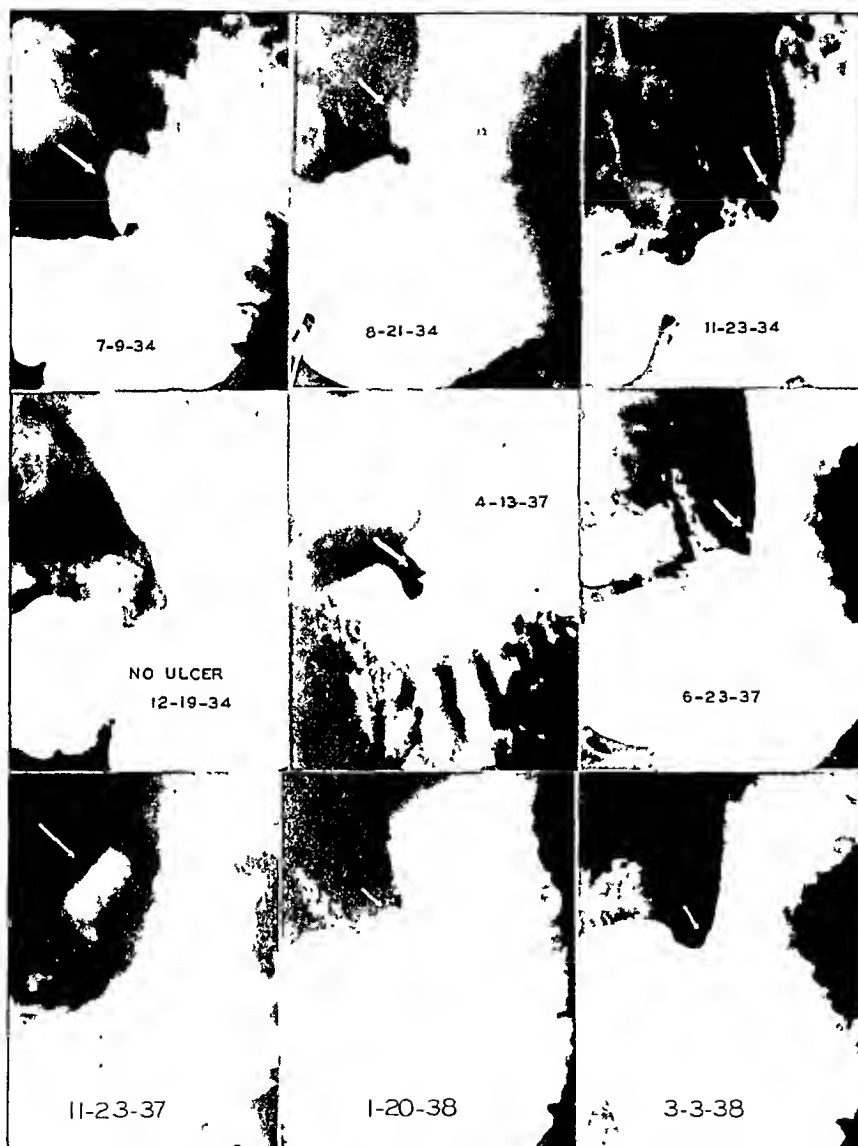


Fig. 9 (Case 11). Note the gradual decrease in the size of the ulcer from July, 1934, to its disappearance in December, 1934; the recurrence at the same site in April, 1937; the progressive increase in size to November, 1937, and the subsequent disappearance of the niche.

familiar with the appearance of the lesion, it was shown that most of these lie in the lesser curvature and slightly on the posterior wall. I have done all my own fluoroscopy in my private practice, for a good many years. I have seen about 570 ulcers in our office. In the last eight years we saw 271. During that period of time we have had a little over forty gastric ulcers, so the incidence between gastric and duodenal ulcer was about 12 or 13 to 1.

We have always been impressed by the difference in the behavior of gastric and duodenal ulcer. It seemed to me that gastric ulcer occurred more suddenly, had a more typical history and, furthermore, on fluoroscopic examination was much more prone to change rapidly, so much so today that we insist in gastric ulcer first on complete bed rest; secondly, on a two-week check-up to observe the crater of the ulcer.

It is interesting to note that Dr. Palmer happened to say, regarding the changes in the size of the crater, changes which neither the condition nor the symptoms of the patient might suggest—it is our own experience that in gastric ulcer recurrence is more frequent. They frequently recur in the same site.

I know one woman from Trenton who had a recurrence four different years in succession, each time on the lesser curvature, each time about as big as the thumb. The question is: What to do to prevent the recurrences, and here in the hospital we take the serious cases with large craters and, if they don't quickly respond to ambulatory treatment, we carry on the drip method. I don't believe any of these, after two weeks with drip method would have gotten any larger, and most of them would get smaller, or altogether disappear.

There is another point that we have discussed all afternoon, the question of peptic ulcer. What does it mean? Is it chronic disease or a *maladie constitutionale*? In any case, I feel we can say: These people have to modify their method of living. They are given a mimeographed sheet, and they take five meals a day always, but beginning around the middle of September, and they are told to take ordinary precaution as well as some neutralizing substance and it is interesting to see how they are controlled. It is the method of living that counts most in the control of the lesion.

Once more I want to express my appreciation of this

CASE 8

A. K., Female, Age 63, Unit No. 148736, X-ray No. 47109

The patient gave a history of epigastric distress appearing thirty years before admission, lasting two years, re-appearing seventeen years later, and then persisting intermittently until her admission to the hospital April 1, 1936. She was discharged on management, symptom-free, April 18, 1936. Her adherence to the treatment was only partial and spasmodic. Slight distress recurred from time to time, and promptly disappeared upon the resumption of a more rigid management. Maximum free acidity (histamine) 49. The roentgenologic and gastroscopic data follow:

X-RAY		GASTROSCOPY		
			Ulcer	Mucosa
4-2-36	Gastric ulcer just below cardia; 5 mm. wide, 4 mm. deep.	4-4-36	Deep penetrating ulcer high on lesser curvature converging folds.	Mucosal hemorrhage, one hemorrhagic erosion.
4-16-36	No crater found.	4-17-36	Ulcer shallow, bleeding.	Small erosion on anterior wall of fornix.
5-27-36	Ulcer in same place, 3 mm. wide, 1 mm. deep.	5-27-36	Ulcer almost healed: star formation of folds.	Slight superficial gastritis above ulcer.
		6-17-36	Ulcer smaller: margins hyperemic; radiating folds.	Slight superficial gastritis above ulcer.
7-17-36	3 mm. wide, depth?	7-17-36	Punched-out, yellow ulcer.	Marked superficial gastritis and antrum.
		8-5-36	Ulcer seen as shallow superficial erosion with five converging folds.	Normal.
10-23-36	10 mm. wide, 10 mm. deep.	10-28-36	Ulcer shallow—about dime size.	Mucosal hemorrhages above ulcer.
12-22-36	3 mm. wide, 3 mm. deep.	12-10-36	Scar or shallow erosion?	Hemorrhages in normal mucosa; slight circumscribed hypertrophic gastritis in fornix.
2-13-37	No ulcer found.			
3-25-37	No ulcer found.	3-17-37	Irregular elliptical small ulcer, radiating folds less marked.	Normal.
		4-14-37	Small erosion at site of former ulcer with marked converging folds.	Normal.
5-15-37	No ulcer—4 mm. niche?	5-12-37	Shallow ulcer about 4 mm. wide.	Mucosal hemorrhage in upper portions.
6-23-37	No ulcer seen.	6-23-37	Crater a little larger.	Chronic hypertrophic gastritis of lesser curvature about the angle.
9-3-37	5 mm. wide, 2 mm. deep.	9-1-37	Crater easily 1 cm. wide	Beginning hour glass.
		12-2-37	Small ulcer, converging folds.	Atrophic gastritis of antrum; beginning hour glass.
1-10-38	No ulcer seen.	1-5-38	Small ulcer.	Slight hypertrophic gastritis in upper part of stomach.
		2-9-38	Healed gastric ulcer scar.	Four mucosal hemorrhages on normal mucosa of lesser curvature.
		2-28-38	Healed ulcer.	Mucosal hemorrhage.
		3-10-38	Normal gastric mucosa.	
3-15-38	No ulcer.	3-29-38	Healed ulcer scar.	No inflammation; hemorrhage of the normal mucosa; first stage of hour glass stomach.

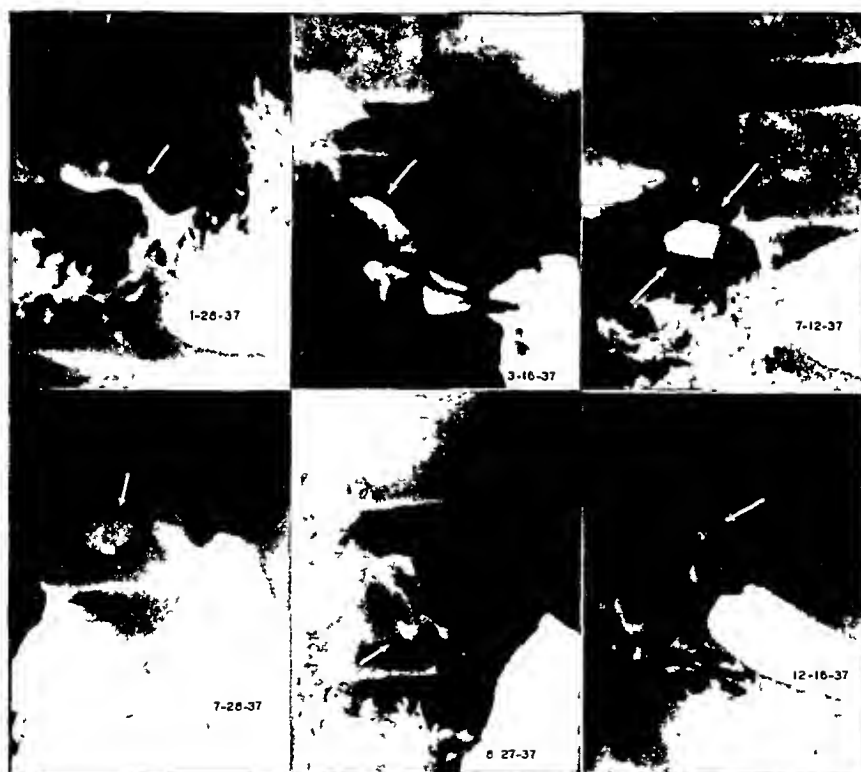


Fig. 10 (R. S., Unit No. 162228, protocol not given): Duodenal Ulcer. Note the definite progressive enlargement of the ulcer from January 28 to July 28 and its subsequent decrease.

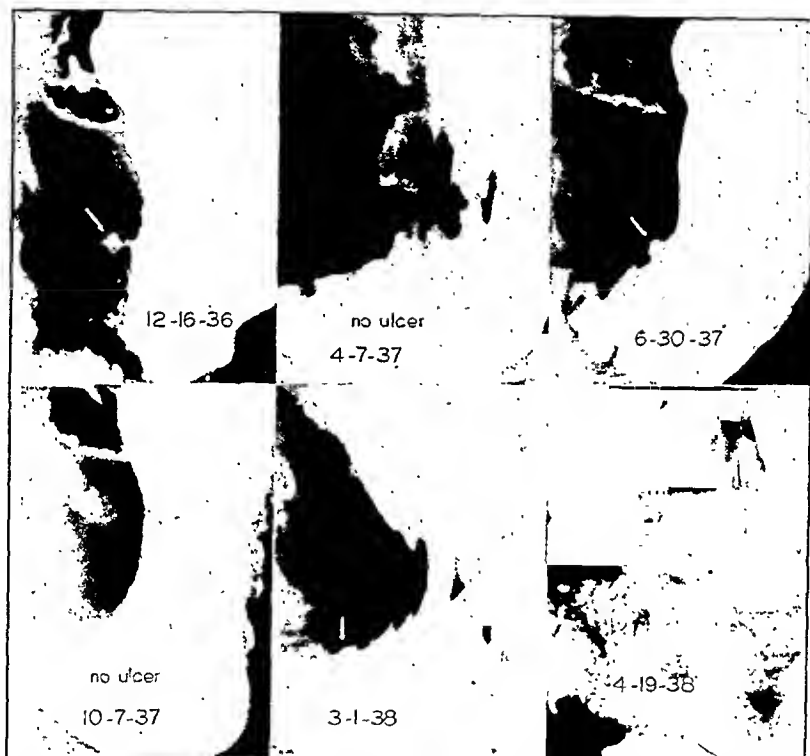


Fig. 11 (Case 12). Note the disappearance of the ulcer from December 16, 1936, to April 7, 1937; its reappearance at the same site June 30, 1937, and disappearance by October 7, 1937; and the appearance of a new ulcer below the angulus March 1, 1938, still present April 19. Gastroscopic confirmation is available for all examinations except that of June 30, 1937.

perfectly beautiful paper. I have never seen a better one.

DR. SARA M. JORDAN (Boston, Mass.): I should like to say a few words to congratulate Dr. Palmer, because to me this paper is a real joy. We are able to corroborate so many of the X-ray findings which he has, showing the recurrence of ulcer, particularly the gastric ulcer, in its original site, also the increase in size of gastric ulcers, but we haven't these striking paintings of the gastroscopic findings which I hope Dr. Wilkerson will help us to get from now on.

The increase in size and the recurrence I think are, in our experience, very definite entities. I should like to ask Dr. Palmer if, when recurrence occurs in a lesion on the posterior wall of the stomach, he becomes alarmed about a change from benignity to malignancy. In two of our cases I am very certain a gastric benign lesion was first present. Later, in the same location, after recurrence of the ulcer twice, a malignant lesion occurred. We, therefore, feel worried about those on the posterior wall because it is often so difficult to heal them after they recur or become adherent to the pancreas.

Dr. Palmer showed us pre-pyloric benign lesions. The benignity of any prepyloric lesion has been disputed so often it is a pleasure to see it so well demonstrated here. We have seen many benign lesions where we have had ample proof they had healed and proved their benignity in that way, and Dr. Palmer has shown us today that in his experience also this is true.

Dr. Sidney Portis in a paper given two years ago, showed by autopsy findings that a pre-pyloric scar was very often present where no pre-pyloric lesion was ever

CASE 9

T. K., Male, Age 52, Unit No. 3265, X-ray No. 1562

When seen on November 19, 1935, the patient gave a history of periodic epigastric distress of ten years' duration. He followed his treatment only fairly well, but did not admit distress in 1936 or 1937 except for a slight amount in September of 1936 in spite of the recurrent crater demonstrated roentgenologically in July, 1936, and again in May, 1937. He developed pulmonary tuberculosis in April, 1937, and then, during hospitalization, followed his ulcer program more faithfully. Maximum free acidity (control aspiration) 60. Gastroscoy was not performed, but the roentgenologic findings are tabulated:

X-RAY		GASTROSCOPY	
		Ulcer	Mucosa
5-25-28	Normal stomach and duodenal bulb.	(Gastroscopy not performed).	
11-19-35	Gastric ulcer, prepyloric, lesser curvature, 10 mm. wide, 5 mm. deep.		
12-17-36	Crater, small, 2 mm. wide, 1 mm. deep.		
1-17-36	Crater estimated as about 4 mm. wide.		
3-10-36	No crater found—marked scarring.		
7-7-36	Recurrent ulcer at same site, 6 mm. wide, 5 mm. deep.		
10-22-36	Crater gone.		
4-29-37	Small crater at original site, 3 mm. wide, 3 mm. deep.		
5-14-37	Crater estimated as 4 mm. wide.		
6-7-37	No ulcer.		
3-24-38	No ulcer.		

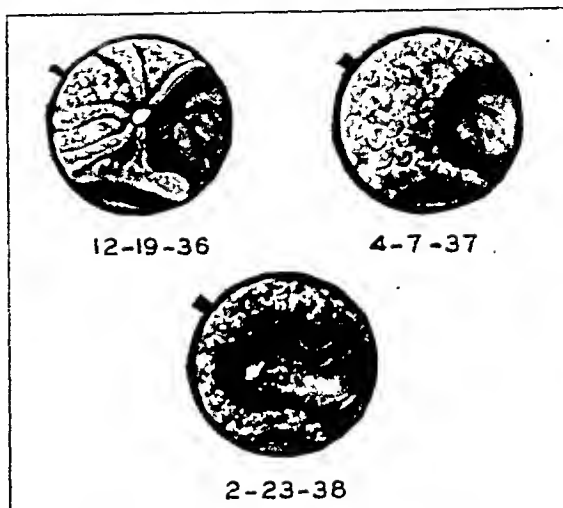


Fig. 12 (Case 12). Note the disappearance of the ulcer on the angulus and the formation of the new ulcer in the antrum. The chronic hypertrophic gastritis is well shown.

suspected from the history of the patient, and that may be of some help in the diagnosis of the pre-pyloric narrowing which Dr. Palmer mentioned. Possibly a small ulcer with scar may have been present there.

DR. CHESTER M. JONES (Boston, Mass.): I should like to raise a question not entirely germane to the subject. In Dr. Schindler's book on gastroscopy, he makes the statement that it is very uncommon and practically a rarity that a peptic ulcer occurs on top of hypertrophic gastritis. It would seem to me, if I have understood Dr. Palmer correctly, that he has presented at least one case which showed just that; namely, a typical, chronic peptic ulcer, occurring in the case of hypertrophic gastritis. It seems to me that it is quite possible for gastric ulcers occasionally to occur on top of a chronic gastritis of the hypertrophic type.

DR. WILLIAM A. SWALM (Philadelphia, Pa.): On the importance of correlating the gastroscopic, the roentgenologic, and clinical diagnoses, we had one difficult case in which there was a gastric ulcer and we saw this gastric ulcer heal up on repeated observations gastroscopically. Subsequently the patient developed a duodenal ulcer, and we were not sure whether the gastric ulcer remained cured. On gastroscopy we found the gastric ulcer had remained healed, and on subsequent observations it has remained healed, and the duodenal ulcer symptoms have been also cleared for the past six months; therefore, I just want to go on record to mention the importance of gastroscopically examining some of these cases.

May I ask one other question? I should like to ask how he feels about the craters of these ulcers, roentgenologically, and anatomically. Are they the same size, and why are they not?

Dr. Ryle of Guy's Hospital in London, showed us a case in which at autopsy the size of the ulcer did not correspond with that seen roentgenologically. I wonder if the essayists can explain this discrepancy.

DR. RUDOLF SCHINDLER (Chicago, Ill.): May I answer the question of Dr. Jones. I still do believe that the small ulcerations of chronic hypertrophic gastritis do not change to true gastric ulcers. I never have observed that, at least, but, on the other hand, in chronic gastritis, the ulcer sites may be surrounded by chronic gastritis, hypertrophic or superficial and even at times atrophic

changes may be seen in the upper portions of the stomach. The question is whether this gastritis is primary and the ulcer is secondary. I believe that the ulcer is primary.

DR. B. B. VINCENT LYON (Philadelphia, Pa.): Entirely from the clinical point of view I should like to ask Dr. Palmer in exhibiting these regressions and exacerbations, enlargements and diminutions, and healing of ulcer in the clinical sense, were these patients treated in what Dr. Palmer would consider an adequate medical sense? If they did this despite adequate medical treatment, then I believe it opens up a new point of view in regard to all of our present ulcer management.

DR. WALTER L. PALMER (Chicago, Ill., closing the discussion): The discussants have been very kind and I wish to thank them, particularly Dr. Jordan and Dr. Rehfuess.

With regard to the question raised by Dr. Jordan, of malignant degeneration of ulcers on the posterior wall, we are very much worried about the possibility that all of these lesions may be malignant until we have had an opportunity to prove them otherwise. I should like to discuss the relationship between gastric ulcer and gastric carcinoma, but there is scarcely time for that this afternoon. Specifically, we have had one case considered to be benign in which death occurred subsequently from gastric carcinoma. For reasons which I cannot give in detail now, the pathologists think that the ulcer was benign and that the carcinoma may have arisen independent of the ulcer. I asked Dr. Wells, specifically, "Do you think in this case there is any reason to believe that the carcinoma arose in the ulcer?" He said he had no way of telling.

The ulcer was an old, penetrating one and the patient died of carcinoma of the type that invades the entire wall and the entire stomach. It seems impossible to decide in this case whether the carcinoma arose in the ulcer or elsewhere in the stomach.

Dr. Schindler has spoken on the question, raised by Dr. Jones, of the relationship between hypertrophic gastritis and ulcer, and I shall not add to that.

With regard to Dr. Swalm's question as to the correlation between the size of the crater as seen roentgenologically and that found anatomically, I had the privilege of discussing this subject with Prof. Hans Heinrich Berg when he was in this country attending the Radiological Congress, and I think it is fair to say he feels there is a definite and exact correspondence if one takes the ulcer immediately after resection and freezes it to prevent the disappearance of edema. When an ulcer is removed at the operating table and fixed a few hours later in the usual fashion, the edema and inflammatory swelling rapidly decrease, and hence the size and depth of the crater in the anatomical specimen appear to differ from the dimensions of the roentgenologic niche more than they actually do.

With regard to Dr. Lyon's question as to whether or not these patients were under adequate treatment, I don't know. I know they were often under what I should consider to be inadequate treatment. The problem, to my mind, is, What is adequate treatment? Usually there was not much difficulty in getting the crater to decrease in size when the patients were in the hospital under controlled conditions. In several of the cases in which the ulcer decreased in size, it did so when the patients came

CASE 10

J. B., Male, Age 65, Unit No. 116703, X-ray No. 36488

The patient gave a story of epigastric distress of six months' duration only. He entered the hospital for treatment November 14, 1934, and was discharged symptom-free December 12, 1934. He has followed a "modified Sippy" program and has not had a definite recurrence of symptoms in spite of the reappearance of the crater in February, 1935, and again in December, 1935. Maximum free acidity (Ewald) 70. The roentgenologic and gastroscopic data follow:

X-RAY		GASTROSCOPY		
			Ulcer	Mucosa
11-19-34	Gastric ulcer 2 cm. proximal to pylorus, 13 mm. wide, 6 mm. deep.	11-21-34	No ulcer seen (pylorus and prepyloric portion of lesser curvature not seen).	Normal.
11-23-34	10 mm. wide, 7 mm. deep.	12-14-34	Benign ulcer, anterior wall near angulus.	One small mucosal hemorrhage; no inflammation.
12-7-34	8 mm. wide, 2 mm. deep.	12-27-34	Depth of ulcer diminished.	Hypertrophic gastritis about ulcer.
12-31-34	No ulcer found.	1-18-35	Ulcer shallower, irregular.	No inflammation about ulcer; slight superficial gastritis of upper parts of lesser curvature.
2-16-35	Ulcer in same place. 2 mm. wide, 6 mm. deep.	3-16-35	No ulcer seen. Pylorus and part of lesser curvature of antrum seen.	Mucosal hemorrhages.
6-29-35	No ulcer found.			
12-14-35	Ulcer at original site. 10 mm. wide, 5 mm. deep.			
2-5-36	Ulcer much smaller. 3 mm. wide, 1 mm. deep.			
4-4-36	No ulcer found.			
10-24-36	No ulcer found.			
2-19-38	No ulcers; good film identical with that of 10-24-36.			

CASE 11

W. R., Male, Age 53, Unit No. 105146, X-ray No. 33471

The patient entered the hospital May 30, 1934, because of hematemesis and melena. Epigastric pain had been present at intervals for many years. In spite of the recurrent ulcer found in a routine examination in April, 1937, symptoms did not appear until November, 1937, when the lesion increased rapidly in size. Complete healing apparently occurred in February, 1938. Deep radiation therapy was administered for ten days in daily doses of approximately 300 r (measured in air) alternately through anterior and posterior portals directed at the upper two-thirds of the stomach, the total dosage being 2953 r, the last treatment being given November 2, 1937. Maximum free acidity (histamine) 94. The roentgenologic and gastroscopic data follow:

X-RAY		GASTROSCOPY		
			Ulcer	Mucosa
7-9-34	Gastric ulcer, lesser curvature, 33 mm. wide, 17 mm. deep.			
8-1-34	20 mm. wide, 9 mm. deep.			
8-21-34	19 mm. wide, 7 mm. deep.	8-21-34	Ulcer, lesser curvature, above angulus with one converging fold.	Slight hypertrophic gastritis above ulcer; one pigment spot, posterior wall.
10-12-34	9 mm. wide, 4 mm. deep.	10-10-34	Ulcer not seen; gray atrophic area thought to be ulcer scar.	Many erosions, lesser curvature, with one flat erosion.
		10-19-34	Small ulcer crater.	Superficial gastritis of whole stomach.
		11-7-34	Ulcer not found.	Gastritis much improved; swollen folds only on lesser curvature.
11-23-34	9 mm. wide, 3 mm. deep.	11-21-34	Ulcer not found.	Gastritis of upper parts of lesser curvature only.
12-19-34	No ulcer.	12-17-34	Ulcer not found.	One small gastritic nodule in anterior wall.
		1-31-35	Ulcer not seen.	Multiple hemorrhages in normal mucosa of lesser curvature and anterior wall.
		7-8-35	Ulcer not seen.	One mucosal hemorrhage, anterior wall.
9-27-35	Radiating folds; scar.	10-30-35	Ulcer not seen.	Normal stomach.
		4-13-35	No ulcer.	Normal.
4-13-37	3 mm. wide, 4 mm. deep.	4-28-37	Two small ulcers at angulus.	No gastritis.
4-23-37	4 mm. wide, 3 mm. deep.	5-12-37	No ulcer seen.	
5-25-37	2 (or 3?) small ulcers, 3 mm. wide, 2 mm. deep.	6-2-37	No ulcer seen.	Extensive hypertrophic gastritis of lesser curvature.
6-23-37	5 mm. wide, 4 mm. deep.	6-23-37	No ulcer seen.	Normal mucosa.
		7-21-37	No ulcer seen.	Normal mucosa.
		9-1-37	No ulcer seen.	Lower third not seen — mucosa normal.
9-22-37	4 mm. wide, 3 mm. deep.	9-29-37	No ulcer seen.	Normal mucosa.
10-21-37	7 mm. wide, 5 mm. deep.	10-27-37	No ulcer seen.	Normal mucosa.
11-23-37	80 mm. wide, 15 mm. deep.	11-22-37	Giant ulcer; diameter estimated at 3.5 cm.	No inflammation; mucosal hemorrhage in normal mucosa.
11-30-37	30 mm. wide, 17 mm. deep.	12-2-37	Gigantic ulcer.	No inflammation.
		12-11-37	Benign healing ulcer with reddened halo, decreasing in size.	
12-21-37	20 mm. wide, 10 mm. deep.	12-20-37	Ulcer decreasing in size.	Slight inflammation about ulcer.
		12-29-37	Ulcer definitely smaller and shallower.	Mucosa normal.
1-5-38	12 mm. wide, 7 mm. deep.	1-10-38	Ulcer definitely smaller and shallower.	Mucosa normal.
1-20-38	8 mm. wide, 5 mm. deep.	1-21-38	Ulcer diameter estimated at 1 cm.	Mucosa normal.
2-3-38	5 mm. wide, 3 mm. deep.	2-11-38	Ulcer very shallow.	Mucosa normal.
2-24-38	2 mm. wide, 2 mm. deep.	2-25-38	Ulcer not seen.	Slight superficial gastritis.
3-3-38	No ulcer.			
4-7-38	No ulcer.	4-5-38	No ulcer seen.	

CASE 12

J. C., Male, Age 31, Unit No. 164495, X-ray No. 53042

The patient gave a history of periodic epigastric pain of eight years' duration with at least two massive hemorrhages. He entered the hospital December 15, 1936, and was discharged January 2, 1937. In spite of "modified Sippy" management, slight distress recurred in March and April, 1937, but was controlled by temporarily returning to the more strict program. In June, 1937, the pain again recurred, but disappeared upon resuming management and has not recurred to date (April 23, 1938) even though the ulcer apparently is not yet completely healed. Deep radiation therapy was administered for ten days in daily doses of approximately 300 r (measured in air), alternately through anterior and posterior portals directed at the upper two-thirds of the stomach, the total dosage being 2951 r, the last treatment being given July 19, 1937. Maximum free acidity (histamine) 75. The roentgenologic and gastroscopic findings were as follows:

X-RAY		GASTROSCOPY		
			Ulcer	Mucosa
12-16-36	Gastric ulcer just above the angulus, 10 mm. wide, 8 mm. deep.	12-19-36	Small ulcer, angulus; perhaps a second ulcer higher on lesser curvature.	Hypertrophic gastritis, posterior wall.
12-31-36	No ulcer.	1-20-37	Healing ulcer.	Marked pallor of mucosa and patchy hypertrophic gastritis.
2-2-37	No ulcer.	2-3-37	Unusual scarring with radiating folds.	Hypertrophic gastritis, lesser curvature about the scar.
4-7-37	No ulcer.	4-7-37	No ulcer.	Marked chronic hypertrophic gastritis, lower third of body, with swollen folds, crevices, and mottling.
6-30-37	Gastric ulcer just above the angulus, 7 mm. wide, 4 mm. deep.	7-14-37	No ulcer.	Hypertrophic gastritis.
10-7-37	No ulcer.	9-20-37	No ulcer.	Mucosal hemorrhages and pigment spots; superficial gastritis after X-ray; minimal atrophic gastritis.
		10-15-37	No ulcer.	
		2-23-38	Ulcer, lesser curvature of antrum beyond angulus.	Severe hypertrophic gastritis about ulcer.
3-1-38	Very small ulcer, about 3 mm. wide, just below the angulus.	3-31-38	Small erosion in place of former ulcer; beginning scarring.	Remnants of gastritis.
4-19-38	Fluoroscopy, no ulcer; film suggests shallow ulcer, 2 mm. wide at angulus.			

Persistent narrowing of the antrum was described in each and every roentgenologic examination.

CASE 13

S. F., Male, Age 47, Unit No. 134295, X-ray No. 42233

The patient, in very broken English, gave an indefinite story of epigastric distress of two years' duration. Roentgenologic examinations were negative in August and October, 1935. Following the roentgenologic and gastroscopic demonstration of a gastric ulcer in March, 1936, ulcer therapy was instituted and complete symptomatic relief obtained, followed by the disappearance of the crater. In December, following a cold, the distress and the crater recurred, but soon disappeared upon the resumption of treatment. The patient then continued a "modified Sippy" program without recurrence of the distress or of the ulcer to date (April 23, 1938). Maximum free acidity (Ewald) 29. The roentgenologic and gastroscopic data follow:

X-RAY		GASTROSCOPY		
			Ulcer	Mucosa
8-13-35	No ulcer; thickened, stiffened rugae suggested gastritis.			
10-28-35	No ulcer.			
3-20-36	Gastric ulcer 3 cm. above angle, 18 mm. wide, 7 mm. deep.	3-20-36	Deep crater-like ulcer above angulus, lesser curvature.	No inflammation around ulcer; slight superficial gastritis around upper part of lesser curvature.
		4-3-36	Ulcer shallower.	One mucosal hemorrhage; superficial gastritis only of upper parts of body.
		4-13-36	Ulcer very shallow; about $\frac{2}{3}$ size of last examination.	Extensive mucosal hemorrhages of anterior and posterior walls of body; no definite gastritis except questionable area around ulcer.
		4-27-36	Ulcer linear, about $\frac{1}{2}$ the size of the first examination.	Two hemorrhagic spots, normal mucous membrane.
		5-18-36	No ulcer; no scar seen.	Four mucosal hemorrhages, lesser curvature.
		6-1-36	Shallow ulcer.	Mucosal hemorrhages.
		7-22-36	No ulcer seen.	Mucosal hemorrhages turning into pigmentation; no inflammation.
		9-9-36	No ulcer or scar seen.	One hemorrhage, middle part of lesser curvature.
11-28-36	No ulcer.			
1-5-37	No ulcer.	1-6-37	Small gastric ulcer 2 cm. above angulus.	Slight gastritis about the ulcer.
1-9-37	Small ulcer, same place, 4 mm. wide, 3 mm. deep.	1-20-37	Very small ulcer, barely visible.	Marked inflammation about the ulcer; hemorrhagic spots along the posterior wall.
2-15-37	Very small depression, 2 mm. wide, 1 mm. deep.	2-17-37	Ulcer not seen.	Mucosal hemorrhages; no inflammation.
2-25-37	No ulcer.			
5-22-37	No ulcer.			
6-23-37	No ulcer.	6-23-37	No ulcer.	Mucosal hemorrhages.
9-3-37	No ulcer.	9-8-37	No ulcer.	Mucosal hemorrhages.
		11-12-37	No ulcer.	Slight hypertrophic gastritis.
3-8-38	No ulcer.	3-2-38	No ulcer.	Normal mucosa.

The ulcer was always seen at the same point—a spot easily seen with the gastroscope. The possibility that it was overlooked or hidden from view, when not seen, seems very remote.

CASE 14

S. B., Male, Age 54, Unit No. 156058, X-ray No. 49673

The patient had an attack of epigastric pain in 1928 and an ulcer of the stomach is said to have been found at X-ray at that time. The pain apparently disappeared on treatment and did not recur until about July 1, 1936. The patient was admitted to the hospital for treatment August 6, 1936, and discharged symptom-free August 18, 1936. He followed treatment for a few months only. Slight distress, recurring in February, 1937, was relieved upon the resumption of therapy for a few months. In November the distress recurred and the patient was hospitalized from December 31, 1936, to January 22, 1938. Deep radiation therapy was administered for ten days in daily doses of approximately 300 r (measured in air), alternately through anterior and posterior portals directed at the upper two-thirds of the stomach, the total dosage being 3066 r, the last treatment being given January 22, 1938. At present (April 23, 1938) the patient is continuing treatment, has no pain, but the ulcer has not yet healed completely. Maximum free acidity (histamine) 102. The roentgenologic and gastroscopic data follow:

X-RAY		GASTROSCOPY		
			Ulcer	Mucosa
7-23-36	Gastric ulcer just above the angle, 11 mm. wide, 5 mm. deep; duodenal deformity, no crater.			
8-7-36	5 mm. wide, 5 mm. deep.	8-12-36	Deep ulcer crater above angulus.	Hypertrophic gastritis about ulcer; hypertrophic node in m. sphincter antri.; patch of atrophic gastritis in upper parts of anterior wall.
9-1-36	Ulcer not found.	10-14-36	No ulcer seen.	Hypertrophic gastritis of almost whole stomach.
12-22-36	No ulcer; duodenal deformity unchanged.	12-23-36	No ulcer seen.	Unusual combination of hypertrophic gastritis with a patch of atrophic gastritis high on the anterior wall.
5-12-37	No ulcer.	5-5-37	No ulcer.	Two erosions; chronic erosive gastritis, lower part near angle on lesser curvature.
9-23-37	No ulcer.	10-6-37	Shallow ulcer, angulus — shallower and smaller than last year.	Chronic hypertrophic gastritis about ulcer.
1-4-38	5 mm. crater.			
1-5-38	No ulcer.			
1-7-38	No ulcer.	1-10-38	No ulcer.	Severe hypertrophic, hemorrhagic, ulcerative gastritis.
1-21-38	No ulcer seen.			
2-12-38	Ulcer 6 mm. wide.	2-11-38	Ulcer at angulus.	Slight superficial gastritis at fornix.
		2-25-38	Ulcer almost healed — very shallow.	Superficial gastritis about ulcer.
3-17-38	Ulcer 6 mm. wide, 2 mm. deep.	3-11-38	No ulcer.	Superficial and hypertrophic gastritis.
		4-1-38	Gastric ulcer of the angulus.	Slight inflammation around the ulcer.

into the hospital and increased when they went home. I became quite annoyed with one lady after that had happened two or three times and gave her a good scolding with instructions to stay strictly on her management with no more running around to bridge parties. The ulcer then healed and has remained healed to date. Whether this was merely coincidence or the result of scolding, I don't know.

In some of the cases in which there were recurrences, the patients seemed to be following treatment as well as they could. We still use the old Sippy program and the patients assured me that although they were going about their work, they were eating a rather soft diet and were taking milk and cream and powders regularly. In one case, while the patient was in the hospital, the ulcer healed very slowly in spite of this regimen. This was one of the cases I showed with marked antral narrowing and gastric

retention. The retention apparently played a very important role in the delayed healing.

I am sorry that I do not have time to discuss the acid factor in the pathogenesis of ulcer and in the mechanism of pain. It came up for discussion earlier this afternoon. I think you have had enough of it; but with regard to pain, one word, if I may. If anyone studying the subject of ulcer pain will carefully take a patient in pain, empty the stomach, wait for the pain to disappear, then inject 200 cc. of 0.5 per cent hydrochloric acid, wait for pain to develop, take the acid out again, wait for the pain to disappear, then put in an alkali, observe that no pain develops, then take it out and put the acid in once more and produce pain again, he can in a few short demonstrations convince himself that acid does have something to do with the production of pain.

Editorials

THE REGULATION OF GASTRIC EMPTYING

WITHIN the past several years great advances have been made in our knowledge of the mechanisms that regulate gastric motor activity. In contrast with an earlier view that gastric peristaltic waves continue uninterrupted throughout the period of digestion and are not subject to regulatory influences we know now that the gastric tone and the force of gastric peristalsis may be changed by many different stimuli when they are applied in adequate strength to the small or large intestine. Among the conditions within the intestine that affect gastric motor activity are mechanical distention, chemical irritation, the action of hypertonic or hypotonic solutions, and the presence in the intestinal lumen of HCl, fat and the products of protein and of starch digestion.

Since the food substances and the products of their digestion, as well as HCl, are present in the normal gastrointestinal contents, any effect that they may have on gastric motility is likely to be physiologically important. The experimental evidence indicates that such is the case. It has been found that the upper intestine manifests a degree of selective irritability toward these particular substances which enables them to exert their specific influence when present in only moderate concentrations.

Hydrochloric acid and some of the products of protein digestion (1) when present in the small intestine act reflexly, through the vagus innervation, to cause inhibition of gastric tone and peristalsis. The response is known as the enterogastric reflex (2). Contrary to current theory, HCl has, apparently, less to do with the regulation of emptying than have the other substances mentioned (1, 3, 4). Quantitative studies (4) have shown that although HCl is an efficient stimulus for the enterogastric reflex (and for temporary reflex closure of the pylorus), it is generally so diluted or neutralized on passing the pylorus that it seldom reaches an effective concentration in the intestine.

Fat in the intestine also causes inhibition of gastric tone and peristalsis. This is an old observation and the slow emptying of fatty meals is well known. More recently Quigley and Phelps (6) have observed a similar effect due to carbohydrate (sugars) in the intestine. The sugars cause marked gastric inhibition only when present in fairly high concentrations and some observers have questioned whether the gastric inhibition is the result of a specific carbohydrate action or of the hypertonicity of the solutions. We have some data (unpublished) which support Quigley's conclusions and we are convinced that certain carbohydrates, at least, have a specific inhibitory effect on gastric peristalsis when they are present in the upper small intestine.

It is possible that fat and carbohydrate stimulate the enterogastric reflex mechanism but the tendency at present is to attribute their action to an inhibitory substance (enterogastrone) (5) which they liberate from the intestinal mucosa. This substance is carried to the stomach by the blood and inhibits gastric tone and peristalsis as well as gastric secretion. It has

been definitely proved (6,7) that fat and carbohydrate may, under certain conditions, exert their specific inhibitory influence through a humoral mechanism.

With these facts in mind we may describe the regulation of gastric emptying somewhat as follows. Some time after food is taken the stomach begins to pour into the duodenum a complex mixture usually containing, among other things, HCl, proteoses and peptones, products of starch digestion and fat. Presently one or more of these substances accumulates in the intestine in sufficient concentration to excite the enterogastric reflex or to start the liberation of enterogastrone. As a consequence, the tone of the gastric muscle diminishes, the intragastric pressure decreases and peristalsis grows weaker; the emptying will proceed at a slower rate. Thereafter the gastric motor activity may be expected to increase if the emptying fails at any time to keep pace with intestinal digestion and absorption, or to decrease if the reverse occurs.

The fact that competent observers have failed to see such fluctuations in gastric activity, and have indeed remarked on their absence, indicates merely that the regulatory mechanism, like other similar devices in the body, accomplishes its function smoothly and efficiently. Probably, once the rate of emptying is adjusted so as to maintain the concentration of gastro-inhibitory substances in the intestine at or slightly above their threshold concentrations, little further change in the degree of gastric activity is required.

Other factors are, of course, involved in the control of gastric emptying. The initial emptying, for example, is probably determined by conditions quite different from those under discussion here. The conditions responsible for the initiation and augmentation of gastric motor activity have not been mentioned although they are obviously essential in the emptying process. However, taking the initial emptying for granted and assuming the constant presence, during digestion, of a gastric "motor drive" we think that the factors which serve to regulate the activity so as to prevent overloading the intestine are comprised chiefly within the gastro-inhibitory reflex and humoral influences resulting from the presence within the intestine of the food materials and the products of their digestion.

J. Earl Thomas, Philadelphia

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THE FORMATION OF HYDROCHLORIC ACID IN THE STOMACH

ONE of the most remarkable chains of chemical reactions in the body is that which results in the formation of the hydrochloric acid of the gastric juice. On one side of the secreting cells is blood with a pH around 7.2, and on the other side is hydrochloric acid

with a pH around 1.5. This means that during the quick passage of material through a tiny gland the hydrogen-ions are concentrated some 700,000 times. Gastro-enterologists would like to learn something of the mechanism which produces this remarkable transformation, if only because if the chemistry of the process were known, they might see where a monkey wrench would conveniently be thrown into the machinery, and then they might have a good cure for ulcer.

Under the microscope it can be seen that, in the large parietal cells, gastric secretion forms in little canaliculi which run through the cytoplasm. At first glance it would seem to be an easy thing to find out with the help of vital stains, reagents, and indicators where the acid is formed and how the precursors of the acid are brought into the secreting cell, but, actually, the difficulties encountered have been so great and the findings so puzzling and so contrary to expectation that knowledge in regard to the phenomenon is still somewhat fragmentary. Much of the early literature will be found summarized in the articles by Collip (1920) and Dawson and Ivy (1926). Unfortunately, some of the early work was not satisfactory, partly because too much time was allowed to elapse between the death of the animal and the staining of the tissue, and partly because the indicators and reagents used were not entirely satisfactory. Some of the indicators probably did not diffuse well into the cells, or they diffused so slowly that, as they entered, other substances had time to diffuse out. Furthermore, some of the indicators and reagents used were injurious to the tissues being studied.

Theoretically the blood must bring to one side of the secreting cell chlorides which are to be split, with extrusion of the base back into the blood and of the chloride ion into the lumen of the gland. Somewhere along the way this chloride must combine with hydrogen. Actually it has been shown by several observers that the blood leaving the stomach is slightly more alkaline than that going to the stomach, and it contains slightly less chloride.

One would expect, on staining the tissues with a suitable reagent, to show large amounts of chlorides entering, filling, or leaving the gastric cells, but actually, the efforts to do this have so far been disappointing. In a recent paper Gersh (1938) described what appears to be the best work done so far on the problem. He studied bits of tissue removed quickly from the stomach of dogs and frozen in liquid nitrogen so as to put a stop instantly to all chemical processes. He found, as López-Suárez (1912) and Lison (1936) had done years ago, that in the resting glands of a fasting animal there is little sign of chlorides in the cytoplasm of any of the five types of cell. Traces could be identified only in the granules of the zymogenic or "chief" cells. Chloride was present in the lumen of the gland along the free border of the cells, and it was present in considerable amounts in the foveola or mouth of the gland and on the surface epithelium. It was evenly distributed through the connective tissue spaces of the lamina propria mucosae and the tela submucosa. Strangely, the distribution of the chloride in the actively secreting mucous membrane did not differ essentially from that in the resting tissue. The only difference was that the amounts were greater.

One possible explanation for these curious and puzzling observations is that the chloride ions are so

closely bound to some protein that they do not combine with the reagent. It is possible also that this hypothetical protein chloride is extruded from the cell as rapidly as it is formed. Curiously, there is no more chloride in the parietal cell than in the supposedly non-acid-forming cells, and as Gerch said, his experiments offer no support to the view that the acid is formed exclusively in the parietal cell.

Collip (1920) concluded from his studies that chloride ions are not taken up by the parietal cells until these cells go into action. He noticed that the interstitial tissue of the mucosa is rich in chlorides and other salts, and he thought that the parietal cells probably drew upon this reservoir. Collip concluded that the cytoplasm of the parietal cells is acid at certain stages of activity, but this he thought was due to the presence of sodium acid phosphate. He was inclined to agree with Maly's theory of the production of hydrochloric acid from sodium chloride and acid sodium phosphate. He doubted if any hydrochloric acid was formed in the parietal cells themselves, but thought it was formed in the canaliculi. In this view he agreed with FitzGerald.

According to Harvey and Bensley (1912-13), who also used a histologic technic, the fluid in the canaliculi of the parietal cells was alkaline, and an acid reaction was found only on the surface of the stomach. They suggested that the parietal cells probably secrete a chloride of some organic base which, on reaching the mouth of the gland, yields free hydrochloric acid.

Dawson and Ivy showed that gastric cells cut off from the circulation change so rapidly in their reactions to indicators that much of the work of the older investigators cannot be trusted. To avoid such postmortem changes Dawson and Ivy injected dye into the living animal and then cut out for immediate examination small sections from the exposed gastric mucosa of a Pavlov pouch. They found that the parietal cells are those most intimately concerned with the elimination of certain dyes from the gastric wall. Unfortunately, a comparison of the chemical structure of the dyes excreted with that of the dyes not excreted did not throw any light on the nature of the chemical processes within the cells. No chemical properties appear to distinguish the one group of dyes from the other. There was no storing of the dyes in the granules of the cells; they apparently were extruded as fast as they entered.

Dawson and Ivy concluded from their studies that both the cytoplasm and the canaliculi of active parietal cells had a pH somewhere between 3 and 6.8. They suggested that there might be a partial dissociation of the hydrogen and chloride atoms from their precursors in the cell and a complete dissociation in the canaliculi or at the surface film separating the cytoplasm from the lumen of the canaliculus. Their evidence suggested that the secretion, as it comes from the parietal cells, must be concentrated in the lumen of the gland perhaps by the absorption of water.

Much against this idea of concentration is the observation by Stöhr (1882), Zimmermann (1925), Harvey and Bensley, and Hoerr and Bensley, to the effect that the secretion as it forms in the canaliculi is viscid and jelly-like. It is coagulable with heat and alcohol, and it stains faintly with Millon's reagent, indicating the presence of tyrosine. As it passes down the lumen of the glands this gummy substance can be seen sometimes to break up into little cylinders or

BOOK REVIEWS

droplets, which eventually are dissolved perhaps by secretions from some of the other cells in the glands. The impression left is that the acid is secreted in the form of a protein hydrochloride which, on being hydrolyzed, yields up the acid.

Recently Bensley, Gersh, and Hoerr decided that a good way in which to get rid of postmortem changes in the cells would be to freeze the tissues instantly in pentane at a temperature of -131°C . or in isopentane at -195°C . Using this technic on material obtained from recently-fed rabbits injected with neutral red, Hoerr and Bensley found the canaliculi of the parietal cells stained a bright yellow, which indicated an alkaline reaction. The cytoplasm was pale yellow, and the contents of the lumen of a gland in its depths was an intense orange-red; from the neck of the gland on out the secretion was crimson, or highly acid.

Because of the possibility that the indicators used do not diffuse satisfactorily into the tissue, the most convincing evidence as to the reaction of the cytoplasm of the parietal cells is that obtained by Chambers when, in 1915, he injected neutral red into these cells with the help of a micropipet. When a very minute drop of dye was injected, it diffused throughout the cell without attacking the nucleus. Soon it faded out of the protoplasm, and orange-yellow or alkaline vacuoles appeared under the edges of the cell. These vacuoles fused to form canaliculi. Within the lumen of the gastric gland there appeared first an orange color which shaded farther along into the red. When the dye was injected directly into the lumen of the gland near the parietal cells, the canaliculi sometimes took on an orange-yellow hue. Farther out in the lumen of the gland the color was a neutral red. These results convinced Chambers that the secretion of the parietal cell is neutral if not actually alkaline. This conclusion is similar to that of Hoerr and Bensley, and French (1918).

Another way of estimating the acid-base balance in the gastric mucosa would be to determine the carbon dioxide equilibrium of the tissue. On doing this Irving and Wilson (1932) found the tension in the resting mucosa to be about 60 mm., and the CO_2 content about 32.0 volumes per cent, which suggests a pH of about 7.0. In an active mucosa the pH may have been slightly

on the acid side. Interestingly, the pH of the acid-forming mucosa in the fundus appeared to be the same as that of the nonacid-forming pyloric mucosa.

The conclusion from all this is that chloride ions accumulate to some extent in the tissues about the gastric cells. They go through these cells so rapidly that no accumulation takes place during the process of secretion. The parietal cells secrete a gummy substance which is probably a protein hydrochloride, and as this goes through the lumen of the gland, it is broken down with the formation of hydrochloric acid. During the process of secretion the cytoplasm of the parietal cell remains practically neutral.

W. C. A.

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Book Reviews

Post-Operative Radiologic Exploration of the Main Biliary Duets (L'exploration radiologique post-opera-toire de la voie biliaire principale). By B. Desplas, P. Moulouguet and P. Malgras. A book of 120 pages with 40 illustrations. Masson & Company, Paris, 1938.

THE X-ray examination of the biliary tract following operation on the gall bladder has been unknown prior to 1922. In recent years, angiocholecystography has appeared very rich in possibilities to surgeons who have experimented with it. Palpation and catheterization of the bile ducts during operation represent much less accurate procedures due to anatomical complexity of the region and to various dangers of introducing a sound, blindly.

In a concise and lucid book, the authors describe their technique of angiocholecystography, the normal

radiological aspects of the biliary tract and their different pathological expressions.

Primarily they discuss the choice of the radio-opaque liquid. After criticism of the different opacifying substances such as bismuth, barium, sodium bromide, thorium, lipiodol, abrodyl, etc. . . preference is given to tenebryl (di-iodo-methane-sulfonate of sodium) used in venous pyelography. Tenebryl avoids inconveniences such as a too high viscosity and opacity met with in the other proposed media.

Instrumentation consists only in a 20 cc. syringe with a display of tips easily connected with the draining tube. The examination should take place between the fourth and tenth day after cholecystotomy. The patient should be kept fasting from the previous evening.

Radiographs should be taken with films over and under the patient, in the supine posture, with the radiation beam centered where the sound penetrates the abdominal wall.

Ten to twenty cubic centimeters of opaque liquid are sufficient in most cases. A skiagram of the region, previous to injection, is recommended in order to reveal a stone eventually overlooked or any other foreign body likely to mislead interpretation.

Immediately after injection, the first film is taken. Then, the catheter is closed with an hemostatic forceps and after a few minutes interval, a second picture is taken, shortly followed by a third film.

Thus, information is obtained on the patency of the bile ducts and on the permanency of really pathological aspects. Cholecystotomy avails best results with cholangiography; but, choledochotomy with the use of a T catheter may also insure good pictures provided certain care is taken.

A thorough knowledge of the normal aspects of the biliary tree is necessary before interpreting the pathological pictures. This requires a rather long training because normal bile ducts are variable.

The injection under the fluoroscope permits an evaluation of the function of the fistulised gall bladder while films bring out accurate anatomical data.

Immediate and remote incidents and accidents of cholangiography present little severity. They are limited to pain during the injection when too high a pressure is used, malaise with nausea, vomiting, subicterus and fever, when a strict fasting has not been observed. Iodism with lipoidal, tenebryl and similar products are not to be feared.

Retention of the substance in the bile ducts is a rare and inconsequential event. The method meets with no other contra-indication except jaundice due to hepatitis.

Following a description of the main and secondary bile ducts, pathological descriptions are exposed with complete details.

Reading and rereading such a book brings out the marvelous possibilities of cholangiography and makes one realize that the pathology of the bile tract is not so simple as usually considered and that everything is not done after the gall bladder has been removed or opened.

With the aid of cholangiography, unrecognized calculi may be detected; patients suffering with severe angiocholitis will be operated on again; residual distention of the main ducts or its stenosis due to coexisting pancreatitis may be discovered; in chronic jaundice by retention without obstruction, the bile tract may be explored so that one can differentiate cases where hepatitis is the only cause from those where choledochitis coexists.

External compression of the terminal choledochus by a cyst or a swelling of the pancreas may be identified; certain biliary or pancreatic cancers, in their

early stages, may be evidenced; finally, in biliary fistulas, the nature and site of the obstacle may be determined while being ignored during operation.

The book contains about forty very good radiograms all clearly explained by annexed drawings.

Albert Jutras, Montreal, Canada.

Introduction a la Chirurgie Digestive. By E. E. Lauwers. Preface—Prof. P. Duval. 220 pages. Masson & Cie, Paris, 1938.

NOWHERE as in this special field shall "functional repair, and not simple anatomical reconstruction, determine the outcome of a surgical intervention of the gastro-intestinal tract."

There is much to be said for this work, which should appeal to the qualified surgeon and those on the threshold of a surgical career in gastro-enterology. The importance of a thorough and extensive knowledge of basic physiological principles which go to build a sound foundation for this "special type" of surgery is stressed throughout the volume, which may be considered more as an essay on function than as a complete study of surgery of the gastro-intestinal tract. Without being too didactic, it has steered a middle course and has unfolded the numerous biological problems instead of describing intricate and non-interesting operative procedures.

This work should prove of material value to the student as well as the experienced surgeon in indicating the numerous pitfalls and problems that this new field presents. The author has proven himself an excellent teacher with a profound knowledge of general surgery and surgical principles, based on the new conception of "physiological versus anatomic surgery."

The author speaks enthusiastically of results obtained by fundusectomy in gastric ulcer and has not been highly elated by results obtained by more radical surgery. Gastro-enterostomy, to most surgeons, seems to be the operation of choice. We do not subscribe entirely to this opinion. A most interesting chapter on cancer of the large bowel includes a discussion of colectomy in one stage, and the better results achieved by Rankin's procedure as compared to the Mikulicz method in dealing with cancer of the transverse or pelvic colon.

Short topics on laboratory tests and explorations of the gastro-intestinal tract, precancerous state, tuberculosis of the intestine, chronic appendicitis, diverticulitis, fistulae of the intestinal tract, and pruritis ani complete the first part of the work.

The second part is given to a short survey of the functional tests for and surgery of the liver and biliary tract, icterus and its classification, and surgery of the pancreas and spleen.

Antonio Cantero, Montreal, Canada.

Abstracts

AMERICAN PUBLIC HEALTH ASSOCIATION

The scientific program of the 67th Annual Meeting of the American Public Health Association in Kansas City, Mo., October 25-28, which will engage the attention of more than 3500 of the nation's health authorities, indicates how closely the organization's Program Committee has been following national trends in public health progress.

There is considerable emphasis on the five major diseases which are being attacked throughout the land with government funds. The grave problem of maternal and infant mortality receives its share of attention. A special session is devoted to a discussion of "Public Health Aspects of Medical Care" which it is expected will be one of the most significant of the entire conference, with exponents of the National Health Program, spokesmen for organized medicine and representatives of the newly-recognized medical consumers, the public, on the platform.

The recruiting and training of public health personnel for the specialized tasks the expansion of health services are creating and for which trained workers are seriously lacking is a major note in the varied program. The health department as a business organization is a new concept which will be treated by the special session method. Administrative procedures, accounting measures, including cost-accounting, will be considered. Many health departments are now on a parity with million-dollar enterprises and special techniques and formulae for the conduct of the big business of public health are definitely needed.

More than 400 papers and reports will be presented and discussed in the four days the public health profession is in convention. The delegates are drawn from every state in the Union, from Canada, Cuba and Mexico and from every branch of public health practice. This makes necessary many individual meetings of the Association's ten sections—Health Officers, Laboratory, Vital Statistics, Public Health Engineering, Industrial Hygiene, Food and Nutrition, Child Hygiene, Public Health Education, Public Health Nursing and Epidemiology—where rock-bottom topics of interest to specialists alone are talked about, and in addition, sessions involving two or more Sections where subjects of broader import cut across the lines of the Section organization. A number of symposia will bring together three

and four of these divisions on such subjects as The Phosphatase Test in the Control of Milk Pasteurization; The Use of Biological Products; Water and Sewage; Frozen Desserts; Typhoid Fever; Pertussis; Nutritional Problems; Industrial Hygiene. Included among the speakers are

such nationally known leaders as Dr. Thomas Parran, Dr. Arthur McCormack, Dr. Abel Wolman, Dr. E. V. McCollum, Dr. Robert S. Breed, Dr. Elliott S. Robinson, Professor C. E. A. Winslow, Dr. I. S. Falk, Dr. Haven Emerson, Dr. Nina Simmonds, Dr. William F. Snow, Major Joel I. Con-

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lessening the absorption of toxic metabolites. In the hands of many of America's outstanding internists Decholin is the medication of choice in chronic cholecystitis, hepatitis of toxic origin, non-calculous cholangitis, and biliary stasis. There is only one contraindication: complete obstruction of the common or the hepatic duct.

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The following organizations are meeting with the American Public Health Association and have prepared programs equally timely and important:

American School Health Association
Conference of State Laboratory Directors
Conference of State Sanitary Engineers
International Society of Medical Health Officers
American Association of State Registration Executives
Association of Women in Public Health.

The American Public Health Association, 50 West 50th Street, New York, N. Y.

EUSTERMAN, GEORGE B.

Chronic, Benign and Small Malignant Ulcerative Lesions of the Stomach: Factors Helpful in the Differential Diagnosis. Radiologic Review, 60:151-156, July, 1938.

In considering the differential diagnosis of small ulcerative lesions of the stomach the author discusses the significance of the roentgenologic findings, gastroscopy, symptoms, age, sex and time of onset, gastric analysis and results of treatment.

The roentgenologic examination, when carried out by a well-trained and experienced roentgenologist, is considered the most valuable single diagnostic agent.

Gastroscopy is of limited value in the diagnosis of early lesions as it is difficult for a diagnosis to be made even on close inspection of the resected specimen. It is only by histologic examination that successful differential diagnosis is possible.

The significance of sex, age, and time of onset is not such as to add materially in the differential diagnosis of benign and malignant lesions.

As regards gastric analysis, mean values for gastric acidity are of little help in differentiating malignant and benign lesions, however the extremes, such as achlorhydria or hyperacidity are of relative value in making the diagnosis.

Progress of the lesion under treatment as determined by repeated observations gives valuable information as to the type of lesion present.

Two charts are included listing the differential diagnostic features of carcinomatous and benign gastric ulcer.

Hanes M. Fowler, Fort Wayne.

AHLQUIST, RICHARD E.

Stones in the Common Bile Duct. Northwest Med., 37:213-217, July, 1938.

The frequency with which stones in the common duct occur without jaundice has not been sufficiently emphasized. Also, the percentage of cases in which stones in the common duct are overlooked at the time of operation on the gall bladder is too high. The general condition of jaundiced patients can be much improved during the preoperative period by the use of a diet high in carbohydrates, adequate fluid intake supplemented by glucose solution intravenously, calcium chloride solution intravenously and blood transfusions.

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1. "The Vitamin B Complex and Functional Chronic Gastro-Intestinal Malfunction: A Study of Two Hundred and Twenty-Seven Cases" by Drs. Borsook, Dougherty, Gould and Kremer, in Am. Jr. of Dig. Dis., June, 1935. Reprint available on request.

2. Relation of Vitamins to Enzymes. J. A. M. A., July 2, 1935, Page 25.

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The values of an infant food can only be judged by composition. Otherwise gross errors in infant feeding occur. When you consider that volume for volume, Karo Syrup furnishes *twice* as many calories as a similar sugar modifier in powdered form, you realize *how* strongly saturated Karo is in calories of maltose-dextrins-dextrose.

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tive period the Trendelenburg position, carbon dioxide and oxygen inhalations, massage of the lower extremities, early passive and active movements, and encouragement of attempt at early coughing have materially lessened pulmonary complications.

Broader and more definite indications for opening and exploring the common duct have materially increased the frequency with which stones have been found.

Adequate exposure, accurate visualization of the common duct preliminary to incising the duct for the purpose of exploration, removal of stones and institution of drainage are essential. Visualization of the

common duct by the injection of a radiopaque solution before the removal of the T-tube is advisable.

Hanes M. Fowler, Fort Wayne.

MILK FACTS

The dairy industry's importance to the national economic system is graphically visualized in the new MILK FACTS booklet issued by the Milk Industry Foundation.

Charts show that the United States is one of the ranking nations in the consumption of dairy products. With per capita consumption of fluid milk at 153 quarts a year, America tops all other countries except Switzerland with 232 quarts.

Annual per capita milk consumption in quarts for other nations is: Denmark, 144; Czechoslovakia, 136; Netherlands, 120; New Zealand, 112; Great Britain, France and Germany, 92; Australia, 88; Belgium, 68 and Italy, 28.

"Milk, in one form or another, comprises over 25 per cent of the 1,500-odd pounds of food used each year by the average American," says the booklet. "It requires about 10½ quarts of milk to make a pound of butter and 4½ quarts to make a pound of cheese. Approximately 350 million new milk bottles are purchased annually.

The booklet contains pictorial charts and figures showing the importance of the milk industry to the country's economic picture. Diagrammatic charts illustrate how the United States utilizes its milk supply of some 48,777,000,000 quarts of milk a year.

Fluid or fresh milk, which provides the farmer's highest cash return, accounts for 29.2 per cent of the country's yearly production. Creamery butter takes 31.6 per cent, farm butter—10.5 per cent, while 12.1 per cent of the milk is used on farms where produced. In making cheese 5.9 per cent of the total milk is used; ice cream—2.3 per cent and canned milks—4.3 per cent, according to charts.

Another chart shows a breakdown of the distributor's milk dollar based on recent certified accountants' figures prepared for the New York legislature. This shows that 44.03 per cent of the dollar goes to dairy farmers for milk; 26.16 per cent to labor; 8.75 per cent for supplies—bottles, cases, trucking, etc.; taxes—2.24 per cent; depreciation—2.40 per cent; profits—2.98 per cent; salaries—less than ¼ of 1 per cent.

"Within less than fifty years," says the booklet, "the production and utilization of milk have so increased in this country that today we are the greatest of dairy nations.

"Milk is our most widely used food, the farmer's largest source of cash income and the basis of an industry which for service and volume has few equals.

"Basic data about the nation's milk supply, the producers and the cows which create the supply, the distributors whose safeguards and efficiency have made wide usage possible and the consumers of this 'most nearly perfect food' are of wide interest.

"Around 25 million cows are milked daily on three quarters of the nation's six million farms—more than 45 million quarts of milk are delivered to homes and stores. Milk, cheese, butter, ice cream and other dairy products create an estimated annual output of 3½ billion dollars.

"The statistical background for this

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RECENT ADVANCES IN THE SCIENCE OF NUTRITION

II. Newer Knowledge of the P-P Factor and the Control of Endemic Pellagra

● The years since 1932, when the P-P factor was known variously as vitamin B₂ or G, have been especially marked by contributions to our knowledge of the anti-pellagic vitamin. Considerable progress has also been made in the treatment of human pellagra as well as in the control of the disease. It might be of interest to review briefly a few of the outstanding developments in this field.

The P-P factor is now accepted as being closely related chemically to nicotinic acid if, indeed, it is not identical with that compound (1). Nicotinic acid has been used successfully in the treatment of human pellagra (2) and there is evidence to support the belief that the P-P factor is intimately associated with essential enzyme reactions in the body (3). A laboratory test has been devised for the early clinical detection of pellagra (4) and there is today better agreement as to the basic dietary requirements for the management of florid pellagra (1).

While the situation as regards endemic pellagra has, in general, shown improvement during recent years, an occasional report indicates that endemic pellagra still constitutes a major medical problem in some localities (5). Authorities agree that the old adage relating to an ounce of prevention being the equal of a pound of cure applies particularly well in the case of pellagra. Consequently, in specific regions of this country certain control measures have been advocated in an endeavor to bring this deficiency disease under permanent control. The most promising of these measures are

the issuance of yeast rations and popular education to the desirability of home production of foods rich in the P-P factor, especially during late winter and early spring. The problem of permanent control of pellagra has been clearly and briefly defined as follows:

"The prevention of endemic pellagra is simple in theory but difficult in practice. If every normal person received enough of the foods containing the pellagra-preventive vitamin there would be no endemic pellagra.—Permanent control can be obtained only by bringing about permanent changes in dietary habits" (1).

The correction of those long-standing dietary malpractices which are responsible for pellagra is certain to be brought about only slowly. The concerted and sustained efforts of all agencies concerned with public health will be required, not only to insure observance of the control measures described above, but also to educate the potential pellagrin to the necessity of a varied diet of protective foods.

Commercially, canned foods may play an important part in the current program designed to bring pellagra under control. Several hundred varieties of canned foods are readily available on every American market at all seasons of the year. Judicious inclusion in the diet of those foods known to be important carriers of the anti-pellagic factor (1) should materially assist in effecting permanent control of endemic pellagra in America.

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- (1) 1938 J. A. M. A. 110, 1665
- (2) 1938 J. A. M. A. 111, 554
- 1938 Ibid. 111, 613
- 1938 B. J. 110, 259

- (3) 1938 J. A. M. A. 111, 25
- (4) 1938 J. Med. Assn. State of Alabama, 8, 52.
- (5) 1939 J. Med. Assn. State of Alabama, 7, 475

This is the forty-first in a series of monthly articles, which summarize, for your convenience, the conclusions about canned foods reached by authorities in nutritional research. We want to make this series valuable to you, so we ask your help. Will you tell us on a post card addressed to the American Can Company, New York, N. Y., what phases of canned foods knowledge are of greatest interest to you? Your suggestions will determine the subject matter of future articles.



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vast industry of wide ramifications should lead to a clearer understanding of milk economies."

NEW MEASURING ROD FOR COMMUNITY HEALTH SERVICES

The American Public Health Association has today issued an APPRAISAL FORM FOR LOCAL HEALTH WORK. The present 200 page document is the result of studies in measuring community needs and community health activities by committees of the Association which have

been continuously engaged in this work for eighteen years.

The Appraisal Form is primarily a measuring rod for community health services. Through the use of a carefully arranged survey schedule the principal health problems of the community are brought to light and defined. The program of community health service in the several fields is analyzed against this background of social and health conditions. The health services as performed are studied in relation to the need with the result that the relative adequacy

of public health work is judged with some consideration of the magnitude and type of local problems.

Heretofore the Association has issued separate schedules for urban and rural work. Advances in rural health practice in the last few years, however, have been so great that the Association believes that issuing separate schedules for the measurement of urban and rural health service tends to accentuate the differences in practice which are rapidly disappearing.

The Appraisal Form is divided into three major sections: a survey schedule for studying a community's health facilities, a schedule for appraising the local health activities, and a list of significant health indices. The Association urges the use of the Appraisal Form by health workers and communities to evaluate periodically and impersonally their public health programs and determine the fields in which change of emphasis may be needed for more effective work.

CORWIN, WARREN C.

Experimental Hypercholesteremia in Dogs. Arch. Path., 26-2, 456, Aug., 1938.

The author takes up again the question of experimental arteriosclerosis in rabbits and guinea pigs due to excess feeding of cholesterol and the fact that it has not thus far been produced in other experimental animals; notably, in cats, dogs, foxes and monkeys.

In order to find out whether a constant hypercholesteremia could be produced in dogs and thereby render this animal a suitable subject for the further study of experimental cholesterol arteriosclerosis, the author conducted experiments on adult dogs in series of varying dietary conditions. First the limits of the cholesterol content of the blood of dogs on a "standard diet" were determined as 185 to 285 mg. per 100 cubic centimeter of blood, and of dogs fed a "kennel diet" as 155 to 240 mg.

Briefly the experimental results can be summarized as follows:

Dogs fed a high fat diet, the fat consisting of 5 to 10 gm. of lard per kilogram of body weight, showed slight but variable increases of the blood cholesterol. Dogs are naturally intolerant to high fat diets and frequently vomit their meals. This fact may have had some influence on the results.

Dogs on a high fat diet plus 3 gm. solid cholesterol in a capsule either with or without sodium cholate, gave the same indifferent results as seen in group 1.

Dogs on a high fat diet to which 10 to 15 gm. of lecithin of adrenal origin was added daily showed a blood

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cholesterol of over 600 mg. per 100 cubic centimeter; and when cholesterol and sodium choline were added in addition the cholesterol values ran to a high of 940 mg.

A second series of experiments under varying dietary conditions corroborated in the main the results of the first experiments. It became evident that a high fat diet is not essential for the development of hypercholesteremia in the dog, and that solid cholesterol added to the diet did not materially alter the results. When lecithin alone was added to either the standard diet or to the kennel diet, elevation of the blood cholesterol took place. When it was added to a high

fat diet it produced a marked hypercholesteremia. This elevation in cholesterol content consisted both of free cholesterol and cholesterol esters.

The experiments were not carried long enough to determine whether arterial changes might occur or not.

N. W. Jones, Portland.

SIMONDS, J. P.

Mode of Origin of Experimental Gastric Ulcer Induced by Cinchophen. Arch. Path., 26-1, 44, July, 1938.

The author reviews the literature on experimental peptic ulcer and concludes from it that in most animals

the gastric mucosa is a very sensitive structure easily injured by a great variety of unrelated agents and that chronic ulcers probably result from acute lesions as a consequence of (a) general nutritional or metabolic disturbances, (b) local functional derangements, (c) continued action of the causative agent or (d) mechanical factors determined by the anatomic location of the acute lesion.

In order to determine if possible the mechanism by which ulcers formed, the author studied the histological changes found in the stomach and duodenum of some fifty dogs and cats which had been fed "old" cinchophen for periods of time from twenty-four hours to over three weeks. The lesions observed in all had as a common characteristic an acute gastritis. This was usually focal and occurred in different forms: (1) edema of a single, or several adjacent, villi; (2) diffuse infiltration of the villi or mucosa with plasma cells and lymphocytes; (3) superficial erosions, sometimes of a single villus; (4) focal accumulations of polymorphonuclear leucocytes above the muscularis mucosae often with liquefactive necrosis; (5) fistula-like channels from these areas to the surface, and (6) large deep ulcers, at times perforated. These lesions were nearly always located in the pylorus and first part of the duodenum.

Hyperacidity played no part in the formation of cinchophen ulcers. As the gastritis always preceded the formation of the ulcer in these instances, the author concludes it must have been an important factor in its causation.

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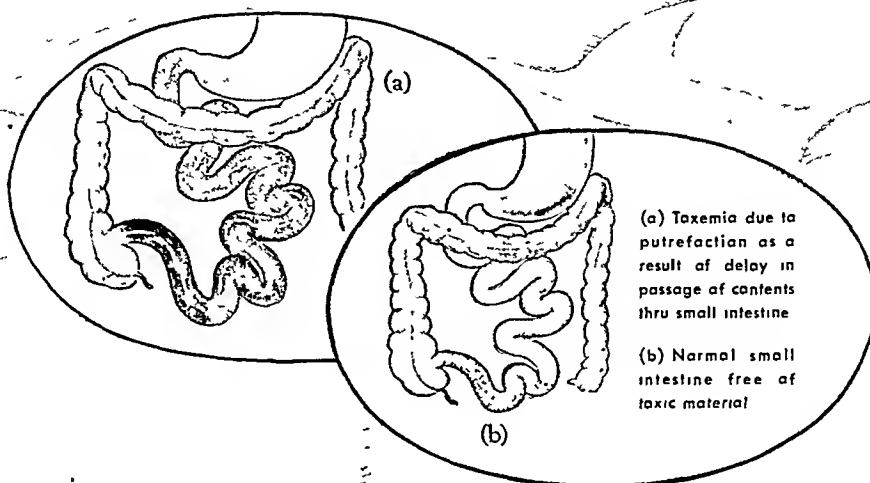
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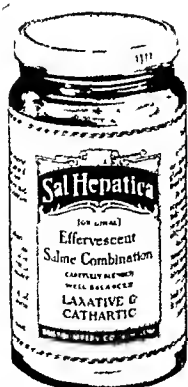
Instrumental Dilatation of the Papilla of Vater. S. G. O., Vol. 66, No. 1, pp. 100-104, Jan., 1938.

Since the histologic structure of the papilla of Vater is approximately the same in the dog as it is in man, the authors studied the effects of instrumental dilatation of the papilla in dogs and drew reasonable conclusions applicable to man.

These studies suggest that damage may be done to the papilla of Vater by instrumental dilatation, such as hemorrhage and inflammation in the acute stages and scarring in the later stages. The end result here is a smaller opening than results from no dilatation at all after cholecystectomy. It appears that the diameter of the papilla, unless scarred, adjusts itself to pressures in the biliary tree within a short time (90 days) after cholecystectomy. Subsequent dilatations after cholecystectomy do not tend to increase the diameter of the papilla. Perfusion pressures in patients who



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have had extensive dilatations of the papilla were higher than those in patients whose ducts were not explored.

The authors believe that it is sufficient to determine the potency of the papilla rather than attempt to dilate it forcibly.

Five figures and a bibliography accompany the article.

Nelson M. Percy, Chicago.

Lake (Brit. Med. Jour., 2:49, 1937) reviewed 320 cases of partial gastrectomy

carried out for the most part for ulcer. Of the 198 cases followed for more than two years there was an unsatisfactory result in only fifteen. The gross mortality was 9.5 per cent in the ulcer cases, 14.8 per cent in the cases of jejunal ulcer, and 14 per cent in the cases of carcinoma. When the ulcer was situated in the pyloric region, the mortality of the operation was but 5.3 per cent. The incidence of jejunal ulcer after partial gastrectomy was less than 2 per cent. No cases of postoperative macrocytic

anemia were observed, but a mild microcytic anemia was seen in a few of the patients after operation. The average duration of life after operation in the patients with carcinoma was 2.25 years.

In the London letter in the Journal of the A. M. A., August 6, 1938, page 549, there is a report of some work by MacGregor on the endocrine treatment of senile vaginitis. Even the gastro-enterologist sees many women after the menopause who complain bitterly of burning in the vagina with perhaps some leukorrhea and perhaps dyspareunia. MacGregor used estradiol benzoate which restored the atrophic vaginal epithelium to a more normal condition. It increased the vascularity of the tissues and promoted healing of areas in which there was a tendency to bleed after denudation of the mucosa. It also helped in restoring the normal vaginal flora. With a cessation of this treatment the vaginal epithelium reverted to its atrophic condition. The drug was given in dosages varying from 5 mg. twice a week to 10 mg. a day according to the severity of the condition and the response. Intramuscular injection was the best method of administration. Suppositories proved disappointing probably because the atrophic condition of the vaginal mucosa interfered with absorption. Suppositories might perhaps have been used with greater benefit after the first doses had improved the local conditions. As a result of treatment eight of the fifteen patients were completely cured and they have remained that way from fourteen to twenty-one months. Vaginal douching should apparently be stopped.

Years ago Whipple and his students showed that over-irradiation with roentgen rays would punch holes in the mucosa of the small bowel. Cathie (Am. J. Roentgenol. and Rnd. Therap., 39:895, 1938) reports two cases out of a series of 400 in which the patients were treated with irradiation for carcinoma of the uterine cervix. In these two cases the patients developed intractable diarrhea and died. At autopsy ulcerations of actinic origin were found throughout the small bowel. The diarrhea appeared during the second week of treatment when only about 1500 roentgens had been delivered. A good many of the other patients had a transient diarrhea which cleared up spontaneously. It is possible that the two patients who did not get well had an idiosyncrasy to irradiation.



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5. The probability of gastro-intestinal irritation is remote.
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Manizade (Wien. klin. Wchnsehr., 50:1455, 1937) examined the blood of 40 patients who from five to twelve years before had submitted to an ex-

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tensive resection of the stomach because of ulcer. In most patients the operation had been performed more than seven years previous to this study. In all cases about two-thirds of the stomach had been removed. Thirty-six of the forty patients had a normal red count and a normal hemoglobin reading. Only four had a blood picture of a microcytic anemia.

Petri and his co-workers (*Acta Med. Scand.*, 93:450, 1937) feel as many others do that pellagra cannot

be explained completely on the basis of an inadequate diet. They saw insane patients in whom pellagra developed in spite of adequate nourishment. They saw also a number of cases in which they felt that they could cure pellagra by the use of extracts made from gastric mucosa. They believe that these extracts have been helpful also in the relief of the polyneuritis associated with alcoholism.

In an interesting paper published

recently, Parsons, Plummer, Ewalt and Gaskill (*J. A. M. A.*, 110:1991-1993, 1938) reported on the incidence of peptic ulcer in patients with syphilis of the central nervous system. As a basis for their study they used records of 200 patients who had clear-cut signs of nervous syphilis. In this group, with an average age of forty-one years, the incidence of peptic ulcer was 10.5 per cent. In another group of 200 patients with an average age of thirty-nine years and ordinary latent syphilis, the incidence of ulcer was 1.5 per cent. One hundred patients averaging thirty-four years of age suffering with pulmonary tuberculosis had an incidence of 1 per cent, while among the general admissions to the hospital the incidence was 3 per cent. In a series of 100 patients with peptic ulcer the incidence of syphilis was 5 per cent.

Because of much evidence showing that disease of the brain tends to be associated with peptic ulcer, it seems probable that the high incidence of ulcer in cases of nervous syphilis is due not to the syphilis but to disease of the brain. The writers doubted if syphilis was the cause of the ulcer in these cases. They admitted that the incidence of peptic ulcer in their series of neurosyphilitics was higher than that reported by other clinicians, but that, of course, might easily be explained on the assumption that their colleagues had taken greater care in examining the stomach roentgenologically.

Lazarus (*Brit. Med. Jour.*, 2:1011, 1937) studied the vitamin C situation in patients with bleeding ulcers. He first measured the amount of cevitamic acid excreted in the urine during a preliminary control period during which the patients were given an adequate diet with extra iron. Patients were then given large amounts of cevitamic acid for four days. Interestingly, none of the patients responded with a significant increase in urinary excretion of the substance, and the impression was that they were not absorbing much of it. Of the twelve patients studied ten were thought to be suffering with vitamin C undernutrition and sub-clinical scurvy. In seven, this lack was thought to be severe. One difficulty with all these studies is that some observers are not yet satisfied with the accuracy of the methods used for determining vitamin C.

W. C. Alvarez, Rochester.

Perazzo (*Arch. Ital. d. Chir.*, 47: 163, 1937) studied graphically the intestinal motility of dogs shortly before and after giving intravenous injections of 15 or 20 cc. of a 20 per cent hypertonic solution of sodium chloride. The injection caused an in-

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**Amer. J. Digestive Diseases*, Vol. 3, No. 4, p. 318, August, 1938

***J. Lab. & Clin. Med.*, 19:327, 1934.

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crease of intestinal tonus and an increase in the amplitude of the pendular movements. This occurred also after bilateral vagotomy. The effect was transitory, lasting from twenty to forty-five minutes. The intestine reacted to a second injection but not to a third one. The author thought that the effect was due to changes of osmotic pressure in the tissues of the intestinal wall. The injection of physiologic sodium chloride solution, or from 6 to 8 cc. of a 20 per cent hypertonic solution did not have any effect.

W. C. Alvarez, Rochester.

At the meeting of the Central Society for Clinical Research (reported in the J. A. M. A., 110:685, 1938) Moore and Arrowsmith reported that iron is transported in the blood stream as serum iron. A new technic has been evolved for the study of the absorption of the iron from the bowel, and it has been shown that following the oral administration of iron, from three to ten times the basal amount in the blood appears in the serum. The authors studied this response in normal persons and also in persons with a histamine-refractory achlorhydria. In the achlorhydric persons they studied the influence of giving iron with hydrochloric acid. When iron is injected directly into the blood stream, all this iron is present in the serum fraction. The authors also studied the disappearance of various types of iron from the blood stream after intravenous injection.

W. C. Alvarez, Rochester.

MAX, H.

The Extent and Character of Peptic Ulcer and Gastroduodenitis in Different Countries. S. G. O., Vol. 66, No. 3, pp. 666-667, March, 1938.

The author points out that geo-medical variations of certain diseases are well known. These variations he has seen within a short distance of 100 to 200 miles in Germany as pertains to the occurrence of gastritis associated with duodenal ulcer. That the same differences may be observed in this country is obvious, as he shows. This probably accounts for the great differences reported in the degree of associated gastritis with duodenal ulcer in this country and in central European areas.

Two cases of gastritis associated with duodenal ulcer are reported.

He concludes that chronic erosive gastritis is more common in certain parts of this country than was previously thought. What parts those are he does not know. He recognized the absence of prohibition as a possible pertinent factor.

Six figures and a bibliography accompany the article.

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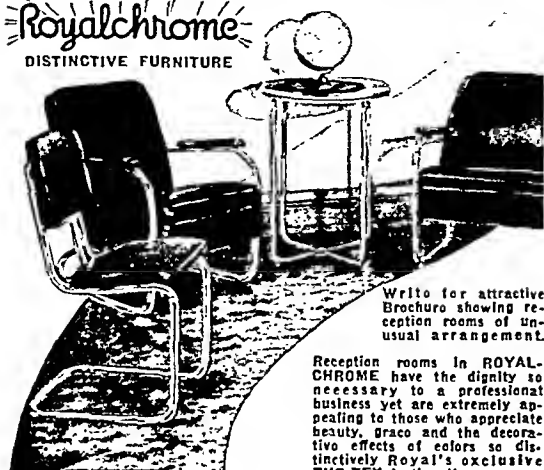
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CONNOTATIONS

H. J. SIMS, M.D.
Denver, Colorado

Paul of Aegina is often credited with having first recognized lead colic; however, Nikander described lead colic and paralysis after injection of excessive amount of lead in writings which appeared in the second century, B.C. Citois describes in 1572 an epidemic of lead colic followed by paralysis. He clinically described the disease. His religious tendency was such that he classed it with other diseases as representative of the wrath of God. Musgrave described in 1703 the symptoms of Devonshire colic. He intimated that it resulted from the use of crude cider. Baker of England read a paper before the College of Physicians on the cause of Devonshire colic, proving that it was the result of lining the cider presses with lead.

The Siamese Twins, Chang and Eng, were born of Chinese parents in Siam, China. They died at the age of sixty-three in North Carolina. Their bodies were joined at a point midway between the umbilicus and ensiform cartilage through which the blood vessels of their liver communicated. They married sisters. Chang was the father of six children and Eng the father of five.

The origin of the term *coll* dates back to 1665, the time of Robert Hooke. He observed spaces in cork which reminded him of minute prisons. Malpighi made the same observation in 1675. Jacob Schleiden published a paper in 1838 in which he described and recognized the importance of the nucleus in cells. He further observed that the nucleus of plant cells represented the mother of new cells and named it the cytoblast. Purkinje first used the term *protoplasm* to describe the cell content. In 1856, Johann Sigismund published an article in which he emphasized the cell as a mass of protoplasm with a nucleus. Eight years later he discovered the prickly cells in stratified squamous epithelium.

The term *retrocolic*, or retroperitoneal appendix, had its inception by Treves who stated in 1885 that the usual position for the appendix was behind the terminal end of the ileum, pointed toward the spleen.

In 1736, Garengnot probably described the first case of a true posterior vaginal hernia. In 1804, Sir Astley Cooper reported the second case. This type of tumor is not to be confused with a rectocele.

Robert Mayer of Germany, had occasion in 1840 to study the blood of people in tropical climates. In 1842, he prepared a paper on the forces of inorganic nature; it was refused publication. Because of his disappointments and adverse criticism, he attempted suicide in 1849. Two years later he was admitted to an insane asylum.

Dr. John Locke of Ohio, demonstrated in 1844 that the tick of a clock could be made to repeat itself over a long distance through a telegraphic media. In 1849, the government called him to Washington to construct the first electrochronograph.

During the time of Pliny, who lived 23-79 A.D., the head of an epileptic was shaved and the area bathed in oils, vinegar, and salt water. When all other methods failed, the drinking of warm blood from a slain gladiator was recommended.

Among the Greeks, epilepsy was known as the disease of Hercules. It is not known why this name was chosen. Some historians insist that Hercules suffered from the disease. Others believed epileptics exhibited superhuman strength during convulsive seizures, and again others accredited the disease to evil spirits.

Hippocrates spoke of the aura of epilepsy, although Pelops, 100 A.D., a pupil of Galen, is often credited with the first recognition. Apamea described the aura in 54 A.D.

In 543 A.D., Aetius of Armida, described lesions of the



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skin, now believed to have been eczema. Willan divided eczema into four classes. Fox of England, differentiated between impetigo and eczema in the year 1864.

Ulcers, especially those occurring on the extremities, were commented upon by Wiseman in 1676. Ulcers were not considered harmful to the patient as it was believed that through ulcers poisonous humors escaped. Wiseman's treatise on ulcers described the advantages of laced stockings. In 1783, Underwood substituted flannel bandages for lincn. Else recommended thin sheets of lead moulded to the contour of the leg as a means of support. Bayton, an English surgeon, suggested the use of strips of plaster prepared by the addition of diachylon to resin. This was melted and applied while warm to strips of bandages. The strips were then wound spirally around the leg.

In 1886, Lawson Tait reported that he had done 139 consecutive ovariectomies without a death.

Previous to 1850, the only attempts made to correct exstrophy of the bladder were those in which mechanical devices were used. The first operation was described by Roux in 1852. Melton in 1854 and Ayres in 1859 borrowed the idea of Roux and used a quadrilateral flap of epidermis with its base attached and its margin sutured to the edge of the bladder.

Most of the information concerning the practice of medicine and surgery among the primitive Mexicans is derived from the writings of Spanish priests. Child-birth was the source of many superstitions. A woman dying in labor was subjected to almost complete mutilation before the body was recovered by relatives. Each portion of the body was believed to be an astrological charm or symbol which would benefit the possessor by exerting magical or occult influence. Many rules were given to the expectant mother. She was cautioned not to expose herself to the rays of the sun and not to chew chicle as the child might

sicken. Any desire on the part of the mother to eat unusual foods must be ignored as food taken by the mother was imparted to the fetus.

Ephraim McDowell, one of the successful pioneers in abdominal surgery, for years had no diploma. He finally received his medical degree in 1825 from the University of Maryland.

CONNOTATIONS

H. J. SIMS, M.D.

Denver, Colorado

It is not certain who originated the transverse abdominal incision. Pfannenstiel, in 1900, introduced a transverse incision through the skin and fascia in gynecological work.

The operation of gastrostomy was proposed by Egbert, in 1837, and first performed by Sédillot, in 1849.

Duse, in 1910, reported an operation for a right-sided hernia. Two testes and an unicornate uterus of infantile type was found in the scrotal sac.

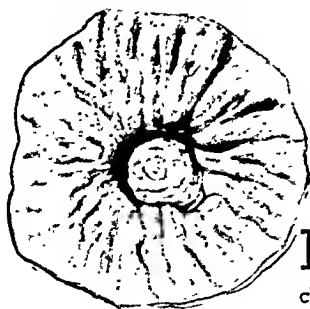
In 1824, Blandin described in an autopsy specimen intestinal herniation through the foramen of Winslow.

A text-book of histology written by Sticker, in 1879, described the bowel as consisting of two tubes, (1) mucous and (2) muscular. Isolation of the submucosa and its importance to surgical anastomosis was made by Lister, in 1881.

Mouchet, in 1898, demonstrated the most common factor as a cause and the rational treatment for surgical relief of ulna nerve palsy.

Roesslin, a German obstetrician, published his text-book in 1513. He gave directions for the delivery of breech and foot presentations and described podalic version. At this time it was believed the foetus breathed through the

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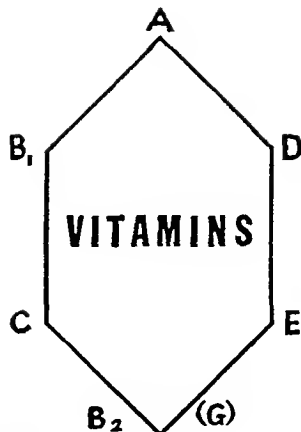
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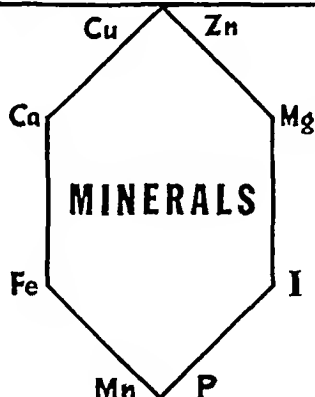
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¹*Southern Medical J., August, 1938.*

²*Report of League of Nations Health Committee, Dec. 6, 1935.*

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vagina. This fact is attested by the directions and method of performing a caesarean section on the dying mother. The mouth of the uterus was held open the moment the patient took her last breath. For stimulation of labor pains the patient inhaled hellebore and ground pepper to induce sneezing.

Legg, in 1910, described the symptoms and roentgen ray findings of a condition now known as "osteochondritis deformans." Perthes, in 1913, gave the disease its present name and differentiated it from juvenile arthritis and tuberculosis.

In 1517, Hans von Gessdorf published a text-book on surgery. He describes himself as a citizen and wound treater of Strassburg. He gives the first illustration of amputation. The patient is seated in a chair. Narcosis was induced by opium. A cord was passed around the leg both above and below the proposed site of amputation. No effort was made to ligate blood vessels. Caustic plasters and the cautery was used to check hemorrhage. The stump was enclosed in the bladder of a bull, ox or hog. He aroused his patients by inhalation of vinegar. He also illustrates a trivalve vaginal speculum. The instrument represents some improvement over a similar one depicted in a text-book of surgery written by Jerome in 1497.

Huneyowski, in 1789, probably recorded the first instance of lateral cervical fistulae.

Mestiver, in 1759, reported a pertyphlitic abscess due to the presence of a needle in the appendix.

Lauger-Villermet described appendicitis gangrenosa in 1824.

The first illustrated book on surgery printed in the English language was by Jerome in 1525.

Pare, in 1522, published his work on surgery. He condemned the use of boiled oil and the cautery to control

hemorrhage. He was unable to obtain boiled oil on a special occasion and substituted a mixture of oil of roses, yolk of eggs and turpentine. His condemnation was in part altruistic.

Richter, in 1762, first suggested the advisability of opening and draining the peritoneal cavity in the presence of general peritonitis. This suggestion was carried out in 1816, by Von Vreeken, in Paris. Sixty years later Kaiser, of Freiburg, was able to collect fifteen cases operated upon.

The first operation undertaken in a known case of perforating ulcer following typhoid fever was carried out by Lucke of Strassburg, in 1887.

To Bollinger, a veterinary surgeon of Munich, is conceded the credit of having first (1877) discovered and described the "ray fungus" as constantly present in, and the cause of the disease called "lumpy jaw" in cattle. Perroncito and Rivolta, Italians, of Pisa, claim to have discovered the fungus in 1868. Harz, of Munich, suggested the name "actinomyces" from the Greek "aktis," a ray, and "mykes," a fungus. Isarel, in 1878, first described the disease in man. He did not differentiate the identity between that disease in man and cattle.

Gas cysts of the intestine were first observed by Colquet and Duvernay in 1825. Such cysts occasionally occur in healthy pigs.

It was fifty years after McDowell performed his first ovariectomy before the French School of Surgery admitted the merits of such a procedure.

Over fifty years ago, Dr. Alexander Goodell ironically remarked, "As the Angels, according to the Schoolmen of the Middle Ages, fly from point to point, without traversing the intervening distance, so, with like swiftness the physician of the present day jumps from any distinctly female ache to an ovarian conclusion."

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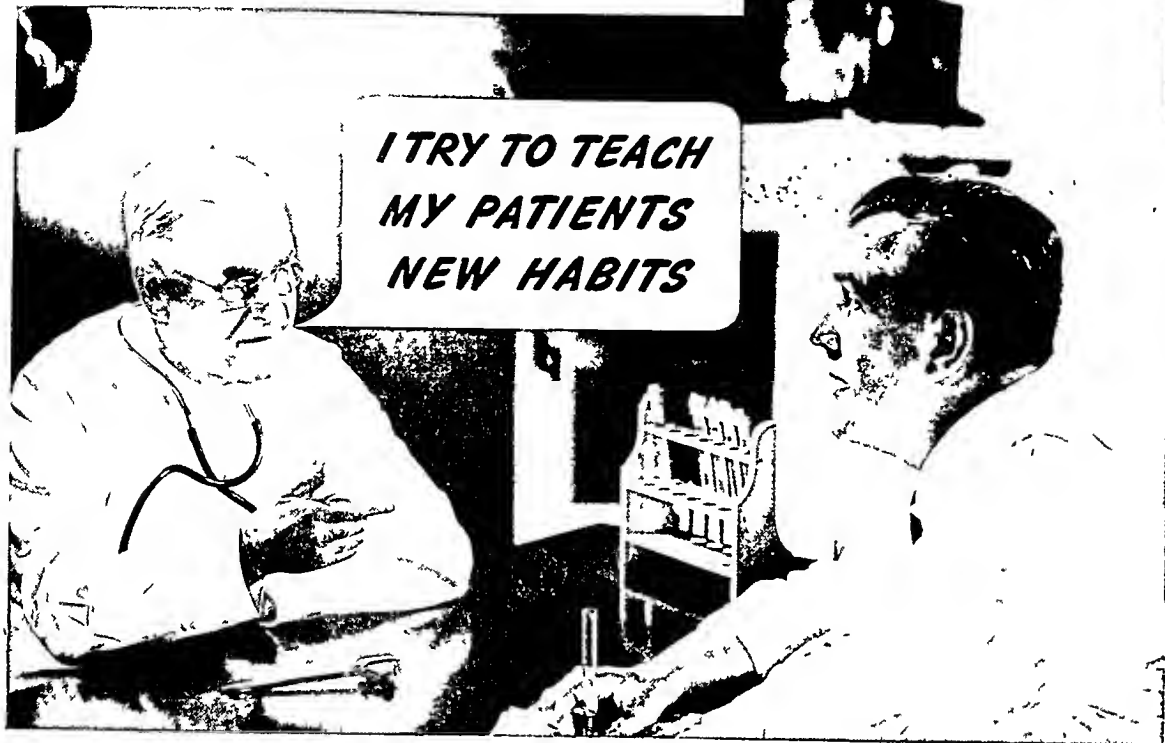
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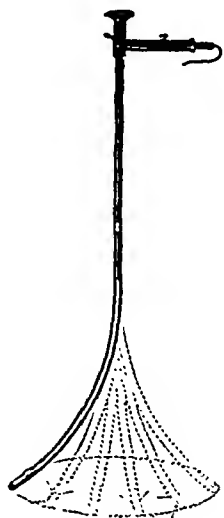
a factor. This includes such conditions as loss of appetite, the toxemias of pregnancy and chronic alcoholism, gastric and duodenal ulcers, and many other common syndromes.

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Early Cancer of the Stomach and its Clinical Significance*

By

WILLIAM CARPENTER MACCARTY, Sr., M.D.
ROCHESTER, MINNESOTA

IN 1827, Bright published his "Memoirs on Abdominal Tumors." He described no cancers of the stomach. In 1894, Osler also reported his experience with abdominal tumors and recorded twenty-four tumors of the stomach; all were large; all the patients were in the last stages of the disease; and all were treated merely palliatively; only one was submitted to surgery and that one died. In 1900, Osler and McCrae reported 150 cancers of the stomach; all were large; all the patients were in the late stages of the disease; and all of them were treated palliatively; only nine were operated upon; six of the nine were explored and

ever seen an early cancer of the stomach; such gastric cancers do not kill their hosts. Any opinions upon the origin of gastric cancer were purely speculative. Not until the operative surgeon began the exploration of living patients was it possible, and probable, for any one to see the early stages of cancer the profession hoped to see. For many years it was only the rare physician who permitted his cancer patient to see the surgeon; the great majority of cancers was hopeless even in the surgeon's hands; only rarely was he able to resect a portion of the stomach. All cancers of that organ were large and as such they really had the text-

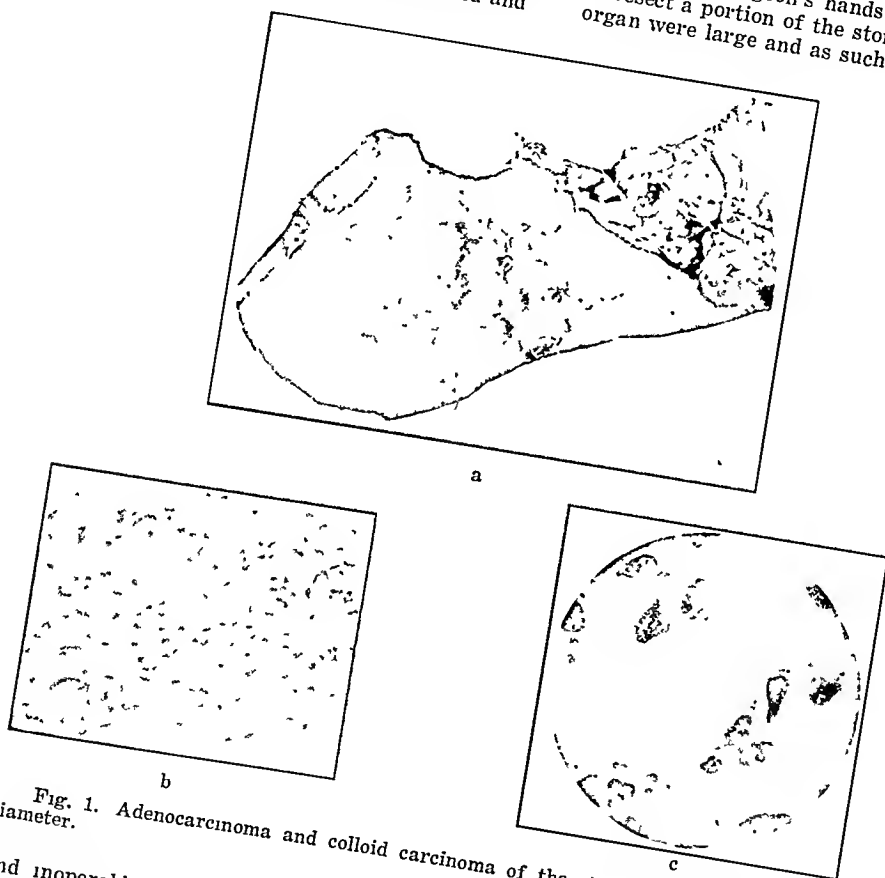


Fig. 1. Adenocarcinoma and colloid carcinoma of the stomach; ulcer 1.5 cm. in diameter.

the condition found inoperable; three of these died and the fate of the other three was not mentioned; one of the remaining three underwent gastro-enterostomy and died, one had a gastrostomy and died, and from the other a growth was removed but the patient died.

Up to 1907, or a few years later, no pathologist had

book signs and symptoms. Then came the roentgenologist beginning his gastric work in the second decade of this century; he visualized the stomach without surgical exploration. Some roentgenologists thought they could differentiate benign ulcers from cancer but the surgical pathologist showed them that in many cases that was impossible. As surgical technique improved, as the immediate operative mortality

*Read before the meeting of the American Gastro-Enterological Association, Atlantic City, New Jersey, May 2, 1938

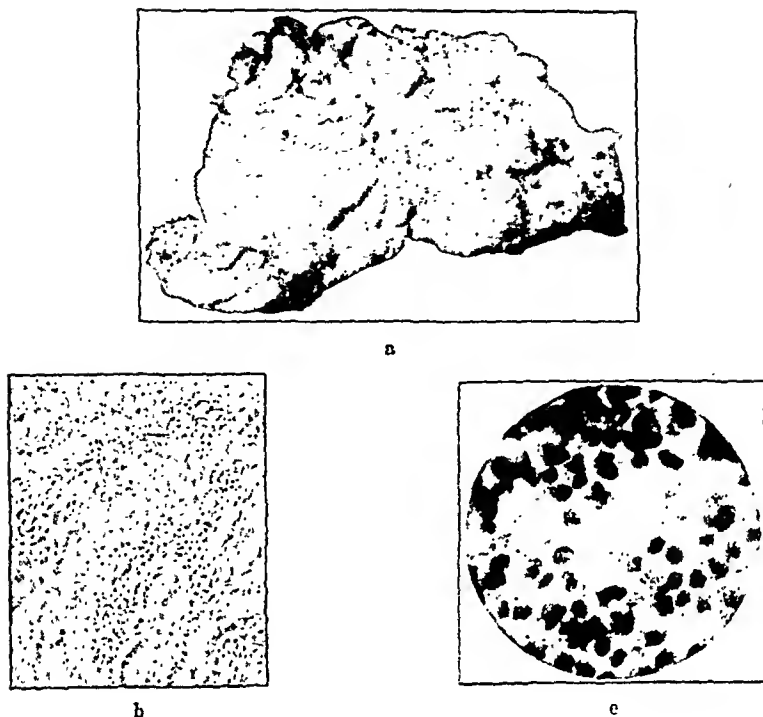


Fig. 2. Adenocarcinoma and colloid carcinoma of the stomach; ulcer 2 cm. in diameter.

became less, and as the roentgenological technique got better, physicians became more willing to submit their epigastric patients to roentgenoscopy and surgical exploration. The surgical pathologist—not the post-mortem pathologist—began to look for small cancers. The surgeon resected some ulcers that were not cancer but neither the physician, roentgenologist nor the surgeon knew these ulcers were not cancer. Such specimens came to the surgical pathologist and some were small cancers.

Today I wish to tell you about 128 small gastric cancers. My first studies on gastric ulcer and cancer were begun in 1907. In 1918 I began the systematic measurement of all gastric cancers. From 1918 to 1931, inclusive, I measured 1568 resected gastric specimens: The average size was 6.1 cm. in diameter and 53 per cent had lymph nodal involvement; six per cent were the size of a quarter (2.5 cm.) or smaller.

From 1931 to 1937, inclusive, I have measured 410 specimens: the average size and percentage of those with lymph nodal involvement are approximately the same as in the earlier series. The frequency of cancers the size of a quarter or smaller has risen from 6 to 9.7 per cent; in 1936 the percentage was 21. In each year of the last six, the percentage was larger than the average for the period between 1918 and 1931.

In the whole series from 1918 to 1937, there were 1978 resected gastric cancers, 123 of which were relatively small cancers (2.5 cm. in diameter or smaller). The questions arise: How were these diagnosed? Did they have pathognomonic signs or symptoms of cancer? Throughout the 128 clinical histories one finds such terms or expressions as pain (dull or sharp,

sudden or burning), weakness, tired feeling, nausea, vomiting, flatulence, bloating, some cruetation, feeling of fullness, indigestion, stomach trouble and periodicity of symptoms. Contrary to the textbook pictures of gastric cancers these cases showed a general absence of such features as emaciation, palpable tumor, anasarca, accessory nodules, cachexia, pallor, edema of the legs, hematemesis, tarry stools and even loss of weight greater than might be explained by a restricted diet. Strangely, also, gastric acidity was high rather than low and the hemoglobin records were normal in the majority of the cases. None of the signs, symptoms, or laboratory findings were pathognomonic of cancer. Such signs and symptoms may be found when no cancer is present, as in simple gastric ulcer, duodenal ulcer, and, frequently, in association with cholecystitis and even appendicitis, brain tumor and syphilis.

Such varied symptoms are fairly common in any group of Americans. Certainly all who have the symptoms do not have cancer, but who has, and who has not, can be determined only by X-ray examinations, sometimes only by surgical exploration, and not infrequently only by microscopic examination. I presume that some of my critics will whisper disparagingly that I would X-ray or surgically explore every one with the slightest indigestion and would even advise that all ulcers should be removed. If they would only whisper a little louder we would see earlier and more curable cancers; at least 75 per cent of the cancers we now see would not be inoperable simply because the X-ray examinations were not made when they should have been. There may be economic reasons for not fluoroscoping or making films of all epigastric

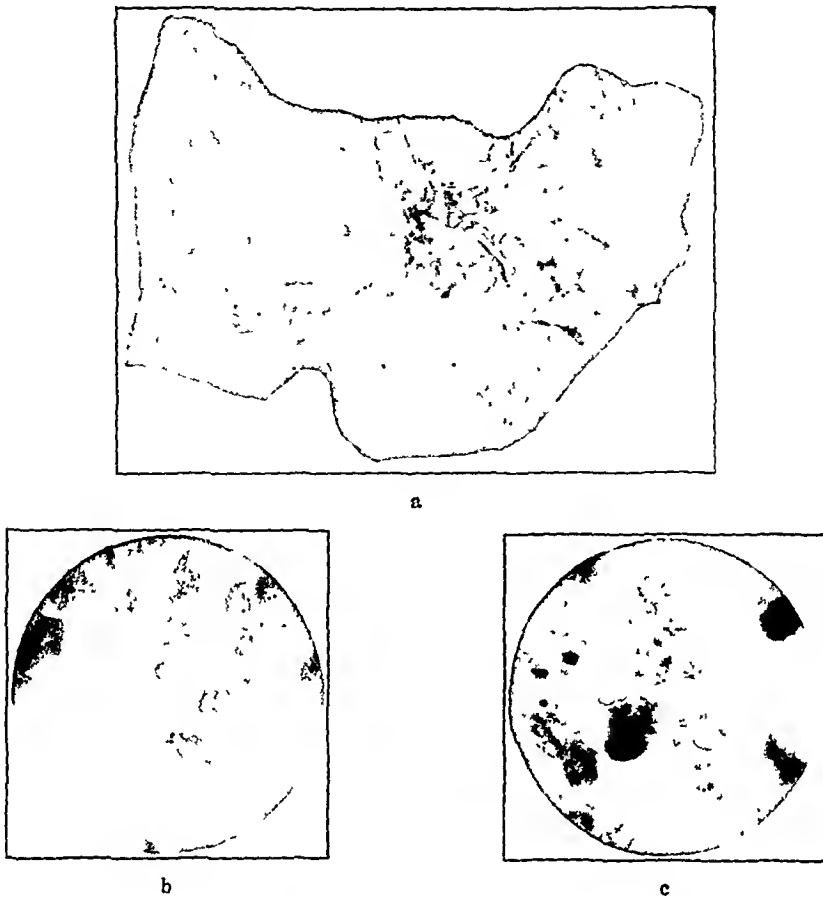


Fig. 3. Carcinoma of the stomach; ulcer 2.5 cm. in diameter.

disturbances but such reasons are rapidly becoming less and less valid. All of the 128 early cancers I am reporting were X-rayed, explored and excised; that is the only reason they were found.

Not until the practicing physician begins to apply, or have such methods applied, will he diagnose cancer of the stomach early. Early cancer has no textbook pathognomonic signs or symptoms and the sooner we appreciate this truth the sooner we shall handle the cancer problem intelligently and successfully.

I have presented this report merely to show that early diagnoses can be, and are being, made with increasing frequency—the frequency being parallel with frequency of thorough clinical study of every case of dyspepsia, indigestion and other mild epigastric disturbances that are now being handled too frequently as of slight significance. The medical profession must appreciate fully that early cancer cannot be found until suspicion, endoscopy, roentgenoscopy, biopsy, and surgical exploration are used very generally as diagnostic procedures.

DISCUSSION

DR. STANLEY P. REIMANN (Philadelphia, Pa.): Mr. Chairman, Ladies and Gentlemen: I begin by paying tribute to Dr. MacCarty for helping us uncover methods for early diagnosis in pathological specimens. I think his work, showing the difference in relative size of nucleolus to nucleus, and so forth, is worthy of great consideration. I always ask myself the question, what does he, what

do I, what do other pathologists try to do when they look at a microscopic specimen. We try to say what would have happened if the surgeon hadn't taken that specimen out. What would it have looked like a month from that time, two months, or three months from that time?

We try to turn ourselves into prophets and a prophet sometimes is not honored much in his own land. We can't tell sometimes because healing processes which take place even in cancer distort cells. They attempt to heal, but are frustrated. How can we tell what they would have done if the surgeon hadn't taken them out when he did?

The crux of the situation lies here: Are these cells distorted because their environment distorted them, or are they distorted because they never could have organized properly even if the environment had given them a chance?

This is the difference, gentlemen, between a cancer cell and a normal cell: The cancer cell cannot, even in this, that, or the other environment, organize into a proper structure, and we try to tell whether that cell or group of cells would have or not by looking at these very early microscopic pictures.

It is true enough when they have displayed their inability to organize by growing down through the submucosa, the muscularis, and the serosa, then we have no doubt, because they tell us, "We can't organize." If, on the other hand, they have not gone that far, are just very early, then it is up to us to guess what they would have done if that specimen had remained there.

These considerations are part and parcel of the dynamic approach to pathology. It is only part and parcel of the idea which can be expressed in any field in pathology.

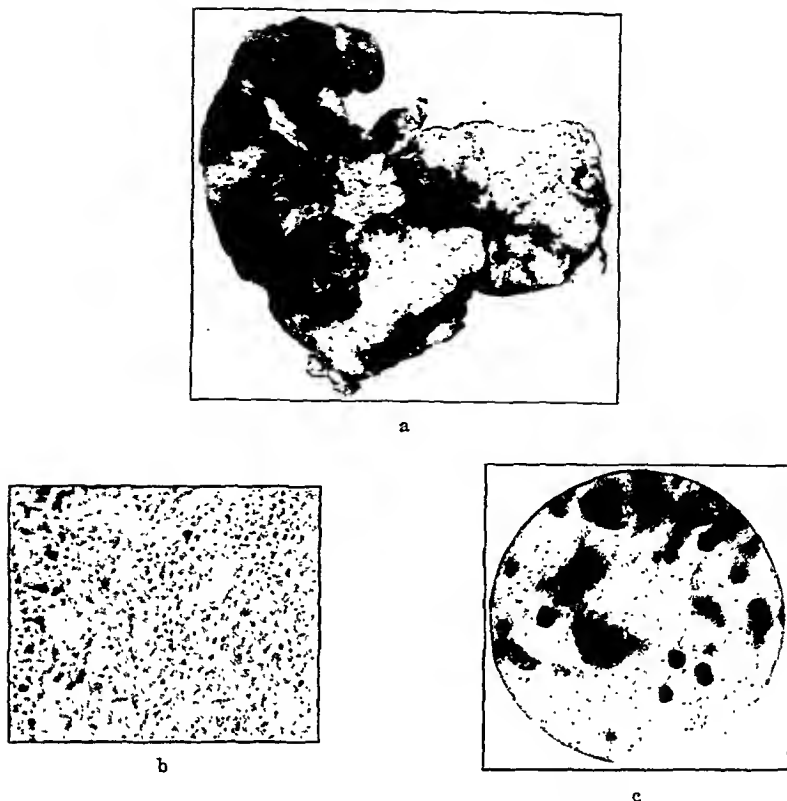


Fig. 4. Carcinoma of the stomach; ulcer 2 cm. in diameter.

What was the picture two weeks ago, four weeks ago, six months ago? What would the picture have been two weeks later, four weeks later, six months later? We can't tell. All we can do is see the cells as of the instant when they were taken out and tossed into a fixative, formaldehyde, Sousa's, whatever fixative is used.

From that point of view, you will see that a great deal of the difficulties in nomenclature and classification—is this or is not cancer—is due to the one fact that we cannot be good prophets.

So far as regeneration is concerned, it occurs in the presence or absence of cancer. The stomach mucosa can regenerate very well. They tell me the sea cucumber, if you tickle or irritate it, will spit his stomach at you, and then sink to the bottom of the sea to grow a new stomach, which would be convenient for some of us. If we had a gastric ulcer, all we would have to do is spit it out and grow a new stomach. Unfortunately, we haven't that ability, but our stomachs do retain a considerable amount of power of regeneration.

Also, the same old question comes up of the influence of heredity and environment, and I was fortunate enough, and so was Dr. MacCarty, to hear Dr. Macklin this morning. I understand she was with you some three years ago. Some interesting new things have come out in her study, especially in relation to gastric carcinoma, and these she presented here. I wish I had time to rehearse one or two of her findings with you.

DR. WALTER L. PALMER (Chicago, Ill.): I have greatly enjoyed this paper. There is one question I should like to ask of the essayist. How many of the 126 patients with small cancers which were resected died subsequently of metastases? I am interested in the question as to

whether or not there are certain types of carcinoma which metastasize so early that we can scarcely hope to get them out before metastases have occurred.

Another question I wish to ask is with regard to healing in gastric carcinoma. Mention has been made several times today of the use of the decrease in size of the crater by X-ray as a differential criterion between benign and malignant ulcer. We have been very much interested in that. Last September I asked Prof. Hans Heinrich Berg if he had ever seen the crater of an ulcerating gastric carcinoma decrease in size. He replied that he had never seen convincing evidence of such a decrease. We have had two cases in which the crater disappeared or decreased in size roentgenologically, and yet the lesion was a carcinoma; however, it has been difficult for us to prove the point because at autopsy the pathologist said, "Well, I think this was originally a benign ulcer and carcinoma arose in the ulcer or elsewhere in the stomach." I would therefore appreciate a statement from Dr. MacCarty with regard to the amount of healing found pathologically in ulcerating gastric carcinomas.

DR. RUDOLF SCHINDLER (Chicago, Ill.): May I mention two considerations concerning early diagnosis of gastric cancer?

First: Evidently it is impossible to diagnose the first change in one or several cells to malignant cells. As long as no super-fine chemical reactions do indicate that there are malignant cells in the body and where they are, we have to depend upon the discovery of gross structural changes in the stomach by ventriculography, X-ray, and gastroscopy; however, in many cases even the early recognition of a malignant growth is of no avail because already as a so-called "early" stage, the tumor is too malignant to

permit complete cure. Therefore, we decided to call an early diagnosis only such diagnosis which would permit cure of long duration.

With this definition, the aspect of early diagnosis in gastric cancer would change entirely. Site, size, and even microscopic structure would become irrelevant; but we found that the diagnosis of the *macroscopic* type, as described by Borrmann is very useful. The Type I, polypoid, circumscribed tumor; and the Type II, localized ulcers with a sharply limited wall, give a good prognosis; Type III, partly infiltrating, malignant ulcers, have a very dubious prognosis; whereas the prognosis of all Type IV carcinomas, the diffuse, infiltrative ones, is not good, even if they are "early" diagnosed (early in the sense in which Dr. MacCarty uses the term).

In my experience the differentiation of these types is more easily made with the gastroscope than by X-ray.

The second remark: The pathologists (Ewing, Staemmler, Bertrand) think that 20 per cent to 50 per cent of all ulcers become malignant. The clinician who watches his patients having a gastric ulcer over a period of five to ten years, never, or almost never sees one of these ulcers turn malignant, if he makes the diagnosis with the gastroscope. If he were to rely only on clinical data or X-ray pictures, he would make mistakes, as was proved by the findings in three cases (but in only three cases) in a series of over 100 gastric cancers; in these three cases, mentioned by Dr. Palmer, the clinical and X-ray diagnosis was that of benign ulcer; the gastroscopic diagnosis, from the very first observation on, was that of a malignancy. These cases, without gastroscopy, would have been considered to be benign ulcers having turned malignant.

If about four per cent of all people die from gastric cancer, then also at least four per cent of all people suffering from gastric ulcer must die from gastric cancer. If the mortality from cancer would be less in this group, we would be forced to assume a protective power of the ulcer-bearing stomach against cancer. I am not willing as yet to admit such a strange power. I hope that in the future the gastroscoping clinicians also will be able to observe the growing of a tumor in at least 4 per cent of their ulcer patients.

I always have pointed out that it is easier to diagnose malignancy in the living tissue as seen through the gastroscope than in the bloodless specimen.

DR. JULIUS FRIEDENWALD (Baltimore, Md.): Dr. MacCarty has very ably discussed one of the most important as well as most difficult diagnostic problems in gastro-enterology.

It is well recognized that the familiar clinical picture of carcinoma of the stomach is that of the advanced disease. However, there are certain early clinical manifestations which may lead at least to a suspicion of this affection. These are:

1. The onset of indigestion in middle life in an individual in previously good health.

2. A supposedly benign disturbance of the stomach in which the characteristic symptoms are altered and become atypical.

3. Continuous absence of free hydrochloric acid in the gastric contents and persistence of blood in the stools.

4. Early evidence of obstruction at the pylorus or cardia.

If in addition to one or more of these, there are signs of gastric retention or roentgenological evidence suggestive of an ulcerating lesion of a type in which the niche, as has been pointed out by Kirklin, is larger than 2.5 cm. in diameter, the diagnosis should be considered as sufficiently established to warrant surgical intervention.

According to our experience, the roentgenological examination is the most valuable diagnostic procedure for determining the presence of carcinoma of the stomach.

In the diagnosis, the chronic ulcer which shows no tendency to heal and the presence of polypi should be regarded as pre-cancerous lesions.

Inasmuch as chronic gastritis is now considered by many as a precursor of cancer, it should likewise be regarded with suspicion when associated with other evidence of cancer.

One of the great difficulties in arriving at an early diagnosis is the fact that a malignant growth of the stomach may at times mimic the symptoms of a benign ulceration; and, in fact, in a small proportion of instances a chronic ulcer may insidiously undergo malignancy.

Again, a considerable number of carcinomatous ulcers occur before middle life, a fact which must be borne in mind in considering the possibility of a neoplasm.

When difficulty arises in differentiating between a chronic benign ulceration and a malignant lesion, I have found the method advocated by Dr. Jordan of the greatest value; that is, the patient is required to remain under close observation and treatment and if a rapid improvement ensues within several weeks, with a disappearance of occult blood in the stools, and especially with a gradual diminution in the size of the ulcer revealed by the X-ray, one can assume that the ulcer is of a benign character; however, if the ulceration shows no tendency to heal under these conditions, even though there is a general improvement in the symptoms, the diagnosis of malignancy must be considered.

Gastroscopy may likewise serve a useful purpose in determining the presence of an early growth.

When one realizes that there is not uncommonly a latent period which may extend over a considerable length of time before any evidence of this disease is manifested during which the growth may attain considerable proportions and the individual may still present the appearance of perfect health, it is easily conceivable how extremely difficult it may often become to arrive at an early diagnosis.

On this account it is important that roentgenological studies be made, if possible, of the digestive tract in the usual periodic health examinations in individuals of over forty years, and especially when affected with even mild chronic digestive symptoms.

As cancer of the stomach is most insidious in its early stages, a re-survey should be made at frequent short intervals in all instances of doubtful digestive disturbances, in order that a definite diagnosis may be reached as early as possible.

In conclusion, it is important, that if doubt as to nature of the gastric affection still remains, surgical exploration should be advised. It is only in this manner that we can hope to determine the presence of this disease at that stage when complete recovery can be expected as the result of surgical intervention.

DR. WILLIAM C. MACCARTY, Sr. (Rochester, Minn., closing the discussion): I wish I had time to talk about all of these discussions. Lots of things could be said, and I am going to summarize Dr. Reimann's discussion, I think, by asking myself a question: Does early cancer always kill? That is approximately what he has in mind. It is a question I have been deeply interested in myself, and I think it is very important not only for the pathologist but also for the clinician. I have the feeling that many of us develop the early stages of cancer and get well.

Dr. Palmer wanted to know how many died in the series. I can't tell him about the 128, but for a period of eleven years I studied part of this series, and 15 per cent of them were known to be dead in the eleven years, and theirs were smaller than a quarter. That may help a little. I am waiting to get the future records of the whole series. I never count anything that isn't definitely cancer that I can prove. I published those figures in *Jour. of Cancer Research*, Vol. xii, No. 1, March, 1928.

About crater decreasing, I feel quite certain that a crater of cancer can decrease under rest. There is a certain amount of inflammatory reaction associated with cancer; this disappears and the lesion becomes smaller.

I could show you records of patients alive after twelve years, in spite of the fact that all the lymph nodes on the specimen were involved.

There should be no great difference of opinion as to what Dr. Palmer and Dr. Schindler are doing with gastroscopy and what I would advise. I don't want anybody to think I am disagreeing with what they are talking about. They are dealing with acute things and with a lot of patients for the first time; many patients should be examined gastroscopically before they get in our hands and give us a chance to cut them out; I know Dr. Schindler feels some of his patients might be cancerous eventually. I am certain some ulcers diagnosed clinically and gastroscopically simple ulcer will be cancer. I would not be surprised if 15 per cent would ultimately turn out to be cancer.

He said something about the characteristics in the floor of a cancer. The early cancers of the stomach do not show in the floor. When a cancer gets in the floor, or the crater of an ulcer, it is very far advanced and is already in the

lymph nodes. The things I am talking about are in the border.

As to my friend, Dr. Friedenwald, I wish all the clinicians in the world were as good a clinician as he is. I often talk about that because so many of the young men today are being taught a lot of laboratory methods and become laboratory clinicians, but after you have seen things for a long while, you become a real clinician, and the changes in the clinical history which he mentioned are certainly very valuable.

I have an idea that early cancer sometimes gets well. Some lions and tigers are relatively benign and quite harmless but I would advise any one who expects to be near one to take along a very high-powered rifle. Expectant treatment in the possible presence of cancer is just about as dangerous as a twenty-two rifle in the presence of lions. I have seen enough small chronic gastric ulcers to make me just as suspicious of cancer as I would be of lions and tigers.

III. The Diagnosis of Colitis Associated With Virus of Lymphogranuloma Venereum by Bowel Antigen*†

By

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With the technical assistance of

BETTY KRAVETZ

BALTIMORE, MARYLAND

MORE than a decade ago, Frei pointed out that when bubo pus, due to the virus of lymphogranuloma venereum, is diluted 1-5 or 1-10 and inactivated, such an antigen will give a characteristic intradermal reaction in those who have been or are affected with this venereal disease. Such an antigen (inactivated bubo pus due to the virus of lymphogranuloma venereum) has become known as the Frei antigen, and the intradermal response to it, the Frei reaction. This immunologic phenomenon is regarded as highly specific.

In many, particularly the males, the disease may terminate as a bubo. In some, especially in women, the virus may descend the pelvic lymphatics and attack the bowel. The tendency is for the bowel process to result in a cicatrizing, fibrosing, stenosing lower rectum with an ulcerative colitis above the stricture. This is the clinical picture as it is usually known; it is the advanced stage of this disease. Not infrequently, however, the clinical picture is not typical: there is the pre-stricture stage and sometimes an ulcerative colitis which is not readily distinguishable from other forms of colitis. Besides, as will be pointed out, the Frei reaction has its limitations in diagnosis. In addition, it has appeared to me that not much greater progress can be expected in the etiology of the indeterminate diarrheas and dysenteries, colitis and enteritis with the present bacteriological and parasitological approaches.

In an attempt to clarify some of these problems, in 1936 I reported (1) intracutaneous responses comparable to positive Frei reactions, with colonic exudate from chronic ulcerative colitis cases with positive Frei reactions. The successful preparation of these bowel antigens was a fortuitous circumstance, and because of technical difficulties noted elsewhere (1, 3) control antigens were not obtainable. The significance of these cutaneous allergic responses, paralleling positive reactions with known active Frei antigens, suggested the presence of an inciting agent unlike a toxin, a specific bacterium or foreign protein, probably the virus of lymphogranuloma venereum or viruses within the intestine of man.

In 1937, improvements in technique due principally to the use of Azochloramid (2), an excellent synthetic bactericidal and bacteriostatic chlorine compound, it was possible to report (3) a dependable, although crude, method of antigen preparation. This resulted in a practical intradermal diagnostic method indicating the presence of the virus of lymphogranuloma venereum in the intestine and differentiating colitis associated with that virus.

This communication reports the securing of eight additional "bowel discharge antigens" and two "bowel (rectal) tissue antigens"* as well as seven control antigens from various sources. The bowel tissue antigens have not been presented by me before. A distinction is being made here between antigens prepared from blood, mucus, pus, bacteria and intestinal contents, grossly fecal-free, heretofore simply called "bowel antigen" and now designated as "Bowel Dis-

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*Thanks is due Mr. Frederick Berry Bang, a third year medical student in the Johns Hopkins University, who secured for me a specimen of bowel tissue for antigen preparation.

charge Antigen," and those prepared from the bowel substance itself, "Bowel Tissue Antigen." The use of this terminology is suggested not only to differentiate types and sources of bowel antigens but to distinguish them from the Frei antigen (inactivated bubo pus due to the virus of lymphogranuloma venereum) and its antigenic response (Frei reaction).

The data to be submitted further establishes, it is believed, the practicability, utility and importance of the method.

PROCEDURES

The method of preparing "bowel discharge antigen" under the previous designation of "bowel antigen" has already been described in detail (3). It is reprinted here for completeness.

I. BOWEL DISCHARGE ANTIGEN:

A. *Preparation of Patient.* Two enemas of physiologic solution of sodium chloride are given, one at bedtime and the other on the following morning a few hours before the rectosigmoidoscopic examination. The purpose is to prevent gross fecal contamination.

B. *Securing of Material.*

1. Devices employed:

(a) A rectosigmoidoscope 1 cm. (three-eighths inch) or 1.6 cm. (five-eighths inch) in diameter and 25 cm. (10 inches) in length is employed, depending on the presence and size of the stricture. An instrument smaller than 1 cm. in diameter does not allow adequate vision and satisfactory insertion of the aspirator. This aspirator is of metal and measures 35 cm. by 8 mm. These are sterilized by boiling. A suction apparatus is also needed.

(b) The receptacle is a glass tube, 15 cm. (6 inches) high by 2.5 cm. (1 inch) in diameter, containing fifteen glass beads. The rubber stopper, glass and rubber connections are sterilized in the autoclave.

2. *Method:* The material, which is usually mucopurulent, frequently bloody, but grossly free from fecal matter, is aspirated by suction into the glass tube containing beads. The prime object is to secure it undiluted and measurable in order to make accurate antigen dilutions; thus, to 1 cc. of the material, 10 cc. of a diluent (Azochloramid, to be referred to later) is added. This is called a 1 to 10 dilution. In most instances this is not possible, for either there is too little exudate or it is very tenacious, too thick or,

sometimes, not visible. Under such circumstances 5 cc. of the diluent is poured through the rectosigmoidoscope and then quickly aspirated.

Aspirated material is vigorously agitated so as to be well mixed and to be broken up into smaller particles.

Whenever dilution in vivo becomes necessary, the subsequent dilutions in vitro in the preparation of antigen become arbitrary, since standardization by weight or volume is impossible; however, the same criteria, to be noted, are employed throughout. Whenever the material is too thick to be readily drawn into a sterile calibrated 10 cc. pipet, it is treated as undiluted and to each cubic centimeter 9 cc. of the diluent is added. It is arbitrarily designated as a 1 in 10 dilution. Material of "medium" consistency is that which can be drawn into a sterile calibrated 10 cc. pipet with facility. Usually, from 3 cc. to 5 cc. of this material is obtained. The diluent is added to make a total volume of 10 cc.

Not infrequently, the aspirated material obtained after the addition of the azochloramid through the rectosigmoidoscope is very thin and translucent, contains little bowel exudate and is mostly diluent. In this case no further dilution is made.

It is to be emphasized that the dilutions are actually higher than indicated, since sodium sulphite and merthiolate—as will be noted—are added.

C. *Preparation of Antigen.* I have already reported the inability to demonstrate the presence of a reaction-producing substance either in filtered bubo pus, a portion of which when unfiltered produces a positive Frei reaction, or in filtered bowel material. Thus, the problem in the preparation of bowel antigen concerns itself with the destruction of bacteria without disturbance of the antigenic factor and with dilution of the material sufficient to decrease foreign protein, so as not to mask the intradermal reaction, and yet insufficient to eliminate for practical purposes the antigenic factor. Also, heating at 60° C. for two hours on one day and one hour on the following day, even in the presence of the bactericidal and bacteriostatic action of the antigen diluent—azochloramid—will not always result in complete bacterial destruction. A higher temperature at 80° C. for one hour is also employed, since I have learned that the antigenic

TABLE I
Master chart: Bowel and control antigens

PATIENTS TESTED	TYPE I Frei +; Ulcerative Colitis						TYPE II Frei -; Ulcerative Colitis without Stricture (1 N ‡)			TYPE III Frei +; Ulcerative Colitis with Stricture (Tissue Antigen) (1 W §) (1 N ‡)			Total with Types I, II, III
	A With Stricture (1 N §) (5 N ‡)			B Without Stricture (1 N §)									
	+	-	Total	+	-	Total	+	-	Total	+	-	Total	
	+	-	Total	+	-	Total	+	-	Total	+	-	Total	
10 N‡ POSITIVE 9 N§ FREI REACTION	33	19	52	10	1	11	3	2	5	5	5	10	78
2 W‡ NEGATIVE 4 W§ FREI 8 N‡ REACTION	0	48	48	0	15	15	0	5	5	0	7	7	77
42 Patients	33	57	100	10	17	27	3	8	11	5	12	17	155

product in bubo pus due to venereal lymphogranuloma will withstand higher temperatures.

The heating is accomplished in the following manner so that at least one antigen will be obtained from a given patient suitable for use in the face of the difficulties referred to:

Equal portions of the material aspirated from the bowel through the rectosigmoidoscope, with or without the addition of 5 cc. of azochloramid, are placed in four sterile 5 or 10 cc. No. 12 army vaccine vials.

Vial A: The contents are diluted either 1 in 10 or 1 to 10 with azochloramid, as already indicated. The vial is sealed with a rubber stopper and collodion and heated in a water bath at 60° C. for two hours, left at room temperature over night and on the following day heated at 60° C. for one hour.

Vial B: The contents are identically diluted and sealed, but the vial is left at room temperature over night to insure the complete action of azochloramid, which is modified by the higher temperature of 80° C. for one hour to which the vial is submitted on the following day.

Vial C: The contents are diluted with half the amount of azochloramid used in vials A and B, and the vial is sealed and heated at 60° C. for two hours. Then, by means of a sterile needle and syringe, the other half of the diluent is added. This vial remains over night at room temperature and on the following day is heated at 60° C. for one hour. The purpose is to supply fresh bactericidal action on organisms surviving both the original supply of azochloramid and the first heating, while making the final dilution no higher than that of the previous antigens.

Vial D: The contents are diluted with half the amount of azochloramid used in vials A and B, and the vial is sealed and left at room temperature over night. Then it is heated at 80° C. for one hour, after which the remaining half of azochloramid is added.

Not infrequently, the material obtained through the rectosigmoidoscope after the necessary addition of 5 cc. of azochloramid is thin, translucent instead of opaque, contains little bowel exudate and is mostly diluent. Equal portions of this material—without further dilution—are placed in two vials. One is heated at 60° C. for two hours and for one hour the

following day. The other is left at room temperature and on the following day is heated at 80° C. for one hour.

In general, the thicker the fecal-free material, the greater is the likelihood of preparing a satisfactory antigen.

In order to dechlorinate the antigens to eliminate the irritating dermal properties and to avoid the carrying over of free chlorine to the sterility test medium, the following procedure is carried out: To azochloramid solution (1:1,666) equivalent to the amount in the vial to be dechlorinated, a sterile, fresh 10 per cent aqueous solution of sodium sulphite is added until the yellow color completely disappears. An equal amount of the sulphite is added to the antigen.

Sterility tests then follow: 0.1 cc. of antigen is placed in 5 cc. of infusion bouillon and incubated aerobically, and 0.1 cc. is inoculated in anaerobic cooked meat medium. The cultures are incubated for seven days. A deep blood agar pour plate is then inoculated with 1 cc. of infusion bouillon culture and incubated aerobically. An anaerobic plate is inoculated with an identical amount from the cooked meat culture, if it is not obviously contaminated, and incubated anaerobically. The plates are incubated for four days.

Merthiolate (1:10,000) is added to each vial immediately after the medium for sterility tests has been inoculated. Not until sterility tests are satisfactorily completed are antigens ready for use.

My experience has been that of the four antigens prepared as outlined in each case, at least one is satisfactory. It is to be reemphasized that this result can be consistently accomplished only by the avoidance of gross fecal contamination.

Although no differences have been noted with antigens heated at varying temperatures and for the durations noted, I have preferred to employ those prepared at 60° C. when obtainable.

II. BOWEL TISSUE ANTIGEN:

A. Preparation of fresh, unfixed tissue:

(1) The tissue is washed thoroughly in tap water and rinsed with 1:1666 solution of Azochloramid.

(2) To each gram (not more than 5.0 grams) 1.0 cc. of 1:1666 Azochloramid in physiologic salt solution

TABLE I CONTINUED

PATIENTS TESTED	TYPE IV			TYPE V						TYPE VI			Total Test Antigens 17 Total Intradermal Tests	
	Frei —; Ulcerative Colitis (Control) (1 W ?) (1 N ?)			Frei —; Carcinoma (Tissue Antigen) (Control) (1 W ?)						Frei —; Generative Tract Discharge (Control) (1 W ?) (2 N ?)				Total with Types IV, V, VI
				A — Ileum			B — Cecum							
				+	—	Total	+	—	Total					
10 N: POSITIVE 9 N: FREI REACTION	17	16	17	0	9	9	0	8	8	1	21	22	55	134
2 W: NEGATIVE 4 W: FREI 8 N: REACTION 9 N:	0	15	15	0	10	10	0	8	8	0	23	23	56	133
	—	—	—	—	—	—	—	—	—	—	—	—	—	—
42 Patients	1	31	32	0	19	19	0	16	16	1	44	45	112	267

W indicates white and N Negro.

± indicates male and ♀ indicates female.

These figures represent single responses to separate antigens; no repetitious test with any antigen on the same patient has been recorded.

is added. It is macerated in a sterile mortar with a pestle and the supernatant fluid removed.

(3) To the residue, the same quantity and strength of Azochloramid, as above noted, was added. The tissue was further macerated and the supernatant fluid was added to that which had been removed previously.

(4) This turbid suspension was placed in a sterile No. 12 Army vaccine vial, sealed with a rubber stopper and collodion and heated in water bath at 60° C. for two hours on one day and for one hour the following day. Sterile precautions were observed throughout. Dechlorinization, sterility tests and addition of merthiolate followed identically as noted above in the preparation of bowel discharge antigen.

B. Preparation of Formalin—Fixed Tissue: (1) Tissue previously fixed in 10% formalin—not in excess of 1.5 grams was left in tap water overnight. (2) It was then rinsed with Azochloramid 1:1666 in physiologic solution of sodium chloride. (3) It was macerated in a sterile mortar with a pestle, and to each gram of tissue ten times the volume of Azochloramid of the strength noted above was added slowly. Thus, to 1.0 gram of tissue, 10 cc. of Azochloramid was used. The latter was added in small quantities during maceration and the resulting suspension was removed from time to time and placed in a sterile vial. The remaining procedures, checking the action of Azochloramid (dechlorinization), sterility tests and the addition of merthiolate for bacteriostatic purposes were identical with those described above.

THE DILUENT AZOCHLORAMID

I have found that Azochloramid destroys all types of intestinal bacteria, both aerobic and anaerobic, in tremendous numbers in dilutions which, on the addition of sodium sulphite, will give no intradermal reactions. It will not destroy the antigenic substance due to or associated with the virus of lymphogranuloma venereum. Its action will not be disturbed at 60° C. and can be checked immediately by the addition of sodium sulphite as noted. Its use made possible the dependable preparation of bowel discharge antigens—

for reasons already noted. (3) With fresh washed or fixed tissue as the material for the antigen, its use was mainly that of destroying possible air contaminants. As composed with physiologic solution of sodium chloride as the diluent, Azochloramid appeared to increase the likelihood of securing antigens free from viable bacteria. This new chlorine compound of unusual properties was introduced by F. C. Schmclkes in 1934. (2).

SOURCES AND TYPES OF ANTIGENS

Type I. Bowel discharge antigens from patients presenting a positive Frei reaction and ulcerative colitis without elephantiasis or vegetations which have been subdivided in the master chart (Table I) as A, those with stricture, and B, without stricture.

Type II. Bowel discharge antigens from a patient presenting a negative Frei reaction (to eight active human Frei antigens) and a colitis with the brunt of the involvement in the rectum, but without stricture.

Type III. Bowel tissue antigens from excised, strictured rectums of those with colitis and positive Frei reactions.

Type IV. Bowel discharge antigens from patients presenting a negative venereal lymphogranuloma history, a negative Frei reaction, with ulcerative colitis without stricture (controls).

Type V. Bowel tissue antigens from fresh, unfixed carcinomatous ileal and cecal tissue (control).

Type VI. Generative tract discharge antigens from three cases presenting negative Frei tests and leucorrhoea. In one the gonococcus was demonstrated; in the others the etiology was undetermined. No history of lymphogranuloma venereum or evidence of colitis was obtainable in this group (controls).

SUBJECTS ON WHOM ANTIGENS WERE TESTED

Intradermal reactions with these antigens were tested on colored and white men and women, with positive and negative Frei reactions, who were free from any active systemic disorder and organic gastrointestinal disease.

TABLE II
Intradermal responses to bowel and control antigens

Type of Antigen	All Intradermal Tests (257)							
	+ Frei (134)				— Frei (123)			
	+	—	Total	%	+	—	Total	False Reaction
I A & B	43	20	53	63.2%	0	64	64	0%
II	8	2	5	60.0%	0	6	6	0%
III	6	5	10	50.0%	0	7	7	0%
				66.6%				0%
Controls								
IV	17	16	17	6.3%	0	15	15	0%
V	0	17	17	0%	0	18	18	0%
VI	1	21	22	4.7%	0	23	23	0%
			Total	3.5%				0%

INTRADERMAL REACTIONS AND INTERPRETATIONS

One-tenth cc. of either type of bowel antigen is injected intradermally, as is the Frei antigen, several specimens of which are tested simultaneously on each patient for comparative purposes. The results are read at nine or ten days. A reaction with the Frei or either type of bowel antigen is considered positive only if its minimal dimension of induration or papule formation in any direction, usually the diameter, is at least 5 mm. Induration is found more often than papule formation with or without necrosis. Induration may extend beyond papule formation, and when this occurs it is included in the measurement. Erythema extending beyond induration and papule formation, or any skin scarification or pigmentation, is not considered in measurement. Induration and papule formation are the basis of measurement. Palpation and careful measurement rather than inspection are important factors in determining results. Experience is essential for proper interpretation, but this is readily acquired. Bowel antigens should be tested on at least three patients known to have a positive reaction to at least one satisfactory Frei antigen and three without any history or evidence of venereal lymphogranuloma and with a negative reaction to multiple Frei antigens. Both groups should be free from any active systemic disorder or any organic gastro-intestinal disease.

RESULTS — COMMENT

The master chart (Table I) is a tabulation of raw data secured by the use of seventeen test antigens of six already described types on forty-two patients totalling 267 intradermal tests. Table II and Table III

TABLE III

Positive responses to individual positive bowel antigens

Antigens	No. of Positive Frei Cases Tested	No. Positive	Per Cent Positive
1. Type IA (1)	10	4	40%
Type IA (2)	10	6	60%
Type IA (3)	7	7	100%
Type IA (4)	10	8	80%
Type IA (5)	8	4	50%
Type IA (6)	8	5	62.5%
2. Type IB (1)	11	10	99.9%
3. Type II (1)	5	3	60%
4. Type III (1)	5	2	40%
Type III (2)	5	3	60%

Positive bowel antigens previously reported

1	10	10	100%
2	10	10	100%
3	13	8	61.5%
4	5	5	100%
5	6	2	33.3%
6	6	4	66.6%
7	5	5	100%

are contractions of data derived from the master chart which are presented for further clarity and to point out the percentages of positive and falsely positive reactions.

Ten positive antigens were realized from ten suspected sources. It should be pointed out that this study is not a study of incidence; it is not a quantitative one. For the purpose of establishing bowel antigen as a diagnostic method, material for antigens was obtained from the most likely sources available. Negroes comprise the vast majority of our material source. They constitute a large portion of the hospital population here, are readily available, and for the most part very cooperative. Thus, it is not to be inferred that this disease is confined almost solely to negroes. The majority of cases reported by Mathewson (4) from San Francisco were among the whites. Few negroes live in Germany and in Scandinavia where the disease is not rare.

Reactions to positive bowel antigens (Types IA and IB, II and III) paralleled the positive Frei reactions in 66.6 per cent of instances (Table II). Reactions to individual antigens of this group varied as follows: Two were positive in 40 per cent of instances tested, one in 50 per cent, three in 60 per cent, one in 62.5 per cent, one in 80 per cent, one in 99.9 per cent and one in 100 per cent (Table III). There were no false positive reactions. In this connection, it is to be noted that individual human Frei antigens also vary in the percentage of positive responses in cases known to be positive to other Frei antigens (Table IV). These variations in bowel and Frei antigens may be due in part to quality and quantity of antigenic substance present and in part upon the individual response to a given "strain." Hence the necessity of using multiple Frei antigens and at least three cases known to be positive to the Frei antigen in testing bowel antigens. In the case of bowel discharge antigen, a "weak" strain may also mean a gradual disappearance of the virus from the seat of involvement: in 1936, the "McK" antigen (1) was positive in 100% of cases giving positive Frei reactions; six months later, with the clinical picture unchanged, another antigen was prepared which gave no responses in cases with positive and negative Frei reactions. A "weak" bowel antigen may also result from the dilution of the antigenic substance in vivo by blood, mucus, pus, bacteria, intestinal contents and sometimes by an accompanying dysentery. Control antigens, Types IV, V and VI averaged false positive reactions in 3.5 per cent of cases with positive Frei reactions. These control antigens gave no false positive reactions in those with negative Frei tests. It is to be emphasized that Type VI antigens (controls) were prepared from vaginal discharges from those with negative Frei tests.

False positive reactions have been markedly reduced in this series of seventeen antigens (Table I) as compared with other antigens previously reported (3). This is believed to be due (1) to the discarding of all bowel discharge evidencing gross fecal contamination in the slightest degree, and (2) to the use of skin test subjects free from any active systemic disease, particularly colitis.

The reasons for believing that a positive bowel antigen indicates the presence of lymphogranuloma venereum virus in the bowel of the person from whose intestinal material the antigen was prepared has been

discussed in detail elsewhere (1, 3). Recently, the following evidence in substantiation has been adduced: uninactivated bowel discharge from which a positive bowel antigen had been obtained was inoculated parenterally into a male dog. Five weeks later the dog tested with two Frei antigens gave positive reactions to both, and a negative reaction to a control antigen of inactivated bubo pus of a non-specific nature. Previous to the administration of the uninactivated bowel discharge, the dog had been negative to three active Frei antigens, one of which produced one of the two positive reactions referred to.* The accompanying photograph (Fig. 1) was taken at the end of ten days. The reactions were still positive at the end of two weeks.

Attention is directed to the results with bowel tissue antigens (Type III). The tissue when submitted for such preparation had already been fixed in formalin. Despite this, one antigen was positive in two of five cases with positive Frei reactions and the other in three of five. They were negative in four and three subjects respectively, with negative Frei reactions. Control antigens from unfixed cecal and ileal malignancy tissue were negative in subjects both with positive and negative Frei reactions. This points out the possibilities in and the desirability of the use of tissue antigen for diagnosis both ante and post mortem, especially since the histopathology is not universally regarded as pathognomonic (4).

TABLE IV

Positive responses to individual human active Frei antigens

Antigen No.	No. Positive Frei Cases Tested	No. Positive	Per Cent Positive
1	14	14	100%
2	11	9	81.8%
3	29	19	65.5%
4	42	35	83.3%
5	11	7	53.5%
6	17	15	94.1%
7	4	3	75%
8	5	5	100%
9	12	11	91.6%
10	10	5	50%
11	8	8	100%
12	15	14	93.3%
13	5	5	100%
14	8	6	75%
15	4	4	100%
16	8	6	75%

The further clinical significance of the use of bowel discharge and bowel tissue antigens does not rest principally on its use from cases presenting colitis, stricture, inguinal scar and positive Frei reaction. These are advanced states and are readily diagnosed. Rather, the importance of bowel antigen rests in the following:

(1) The limitation of the Frei reaction:

(a) Anergy. This is a well known immunologic phenomenon (5, 6). A number of lymphogranuloma venereum cases do not give positive Frei reactions with multiple active human antigens. This problem may not be troublesome where the case presents a typical clinical picture. However, this does not account for those cases presenting negative Frei reactions and clinical states less typical or indistinguishable from those brought about by other agents and in whom anergy can only be detected after a positive bowel antigen has been obtained. An example will suffice. A negress, negative to eight active human Frei antigens, presented a colitis without stricture, whose bowel discharge antigen (Type II) gave three positive re-

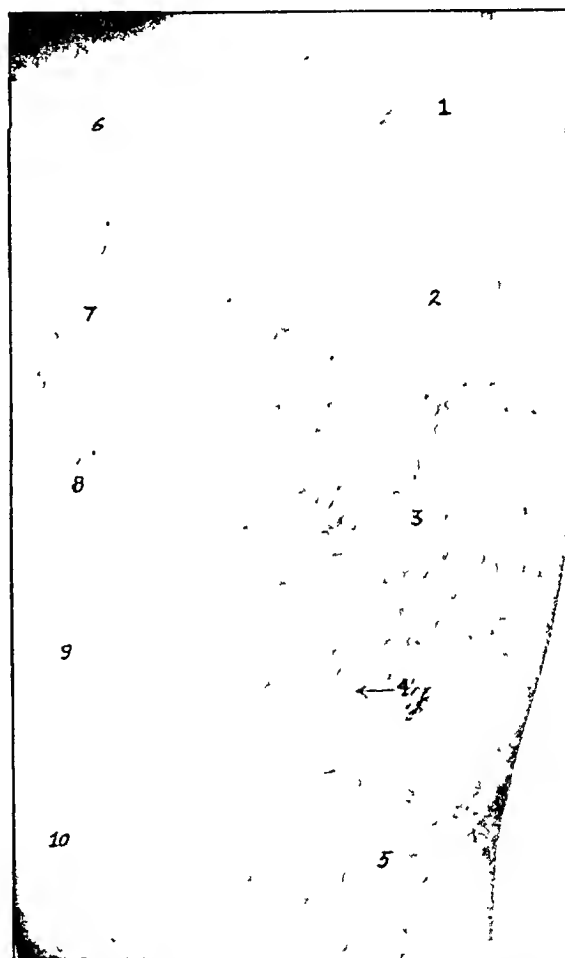


Fig. 1. Examples of intradermal reactions to bowel antigens. Colored male with positive Frei reaction with no active systemic or organic gastro-intestinal disease. Responses were read at 9 days. 1 is a positive reaction to positive bowel discharge antigen, Type IB. 2, 3 and 4 are positive reactions to positive bowel discharge antigens included in Type IA. 5 and 6 are negative responses to control tissue antigens, Type V. 7 is a positive reaction to a 1:5 dilution of active human Frei antigen. 8 is a negative response to a control bowel discharge antigen included in Type IV. 9 is a positive response to a positive generative tract (vaginal) discharge antigen (to be reported). 10 is a negative response to a control generative tract (vaginal) discharge included in Type VI.

*Thanks are due to Dr. Ferdinand C. Lee, Associate Professor of Surgery, Johns Hopkins University (in charge Surgical Hunterian Laboratory) for opportunities afforded to pursue this phase of the work.

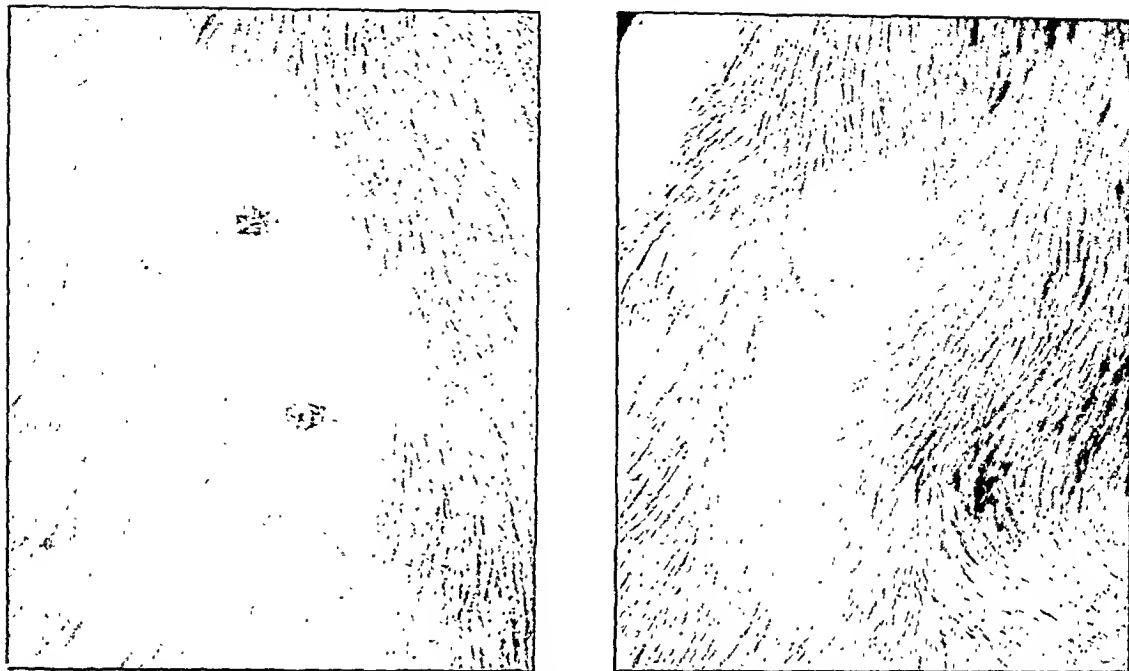


Fig. 2. Positive reactions in a male dog with two active human Frei antigens at 10 days following the parenteral injection of unactivated bowel discharge from a patient from whom a positive bowel discharge antigen had been obtained. Prior to bowel discharge administration, the dog was negative to 3 active Frei antigens, one of which produced one of the two positive reactions shown. These positive reactions were as pronounced at 14 days. The control antigen consisting of inactivated bubo pus of non-specific origin from several human sources produced no reaction. This, it is believed, helps further to establish that the virus is present in material from which a positive bowel antigen is secured, and the skin response is brought about either by the inactivated virus or an associated product.

actions in five cases with positive Frei tests and no reactions in six cases with negative Frei tests (Table III).

(b) The Frei reaction may represent an antedated, healed or unrelated virus infection. A positive bowel antigen is a more specific, and a more direct diagnostic test. A case in point is that represented by bowel discharge antigen Type IB. A colored male with a positive Frei reaction developed a typical ulcerative colitis without stricture three years after the bubo involvement. Was the intestinal affection unrelated to his venereal disease? The answer rests on the fact that ten of eleven cases with positive Frei reactions were positive with his bowel discharge antigen; sixteen cases with negative Frei tests were negative to it.

(2) Bowel antigen may be important from a public health standpoint. Those indicating the presence of virus by a positive bowel antigen would seem to be public health menaces, in the sense that the extrusion of any material containing the virus may by contact disseminate this agent. The positive Frei reaction does not necessarily indicate the presence of virus in the bowel; the virus may never have been associated with the colitis or enteritis, or it may have disappeared from the intestinal involvement.

(3) The trend of experimental and clinical evidence points towards this virus as being a cause of the colitis with which it is associated (7). Because of the limitations of the Frei reaction, the bowel antigen is the only practical method at present which will demon-

strate the presence of this agent in the involvement.

(4) A positive bowel antigen secured especially from those in whom the clinical picture is not typical of the advanced stage of colonic involvement by this virus, the stage most widely known, would result in a different clinical approach to the problem.

A bowel antigen producing no reactions may indicate the absence of the virus or its presence in too small an amount in the material obtained for antigen purposes. If it is felt that the latter might be true, another attempt to secure more suitable material should be made.

A satisfactory positive bowel discharge antigen such as Type IB can be used in place of a Frei antigen. The bowel infection persisting for a much longer period results in a more constant source and obviates to some extent the difficulties surrounding the obtaining of adequate bubo pus from human beings.

SUMMARY AND CONCLUSIONS

1. Two positive bowel tissue and eight additional positive bowel discharge antigens, as well as seven control antigens from various sources are reported. Positive responses to bowel antigens indicate the presence of the virus of venereal lymphogranuloma in the material from which the antigen was made. Further proof in substantiation has been adduced by the production of positive Frei reactions in a male dog inoculated with unactivated bowel discharge from a patient from whom a positive bowel discharge antigen had been obtained. The trend of experimental and

clinical evidence points toward this virus as being a cause of the colitis with which it is associated.

2. A new method for the practical preparation and use of antigen of ante and post mortem bowel tissue is presented.

3. Bowel discharge and bowel tissue antigens render the diagnosis of lymphogranuloma venereum infection in the bowel more direct and specific and is important for the following reasons:

(a) The limitations of the Frei reaction as exemplified by anergy, and by the fact that the Frei reaction will not establish the presence of the virus in the bowel; also, the Frei reaction may be present as a result of a healed or unrelated infection.

(b) From a public health standpoint, since patients from whom a positive bowel antigen is secured would seem to be menaces. The positive Frei reaction does not necessarily indicate the presence of virus in the bowel.

(c) A positive bowel antigen secured especially from those in whom the clinical picture is not typical of the advanced state of bowel infection by the virus of lymphogranuloma venereum as it is generally known, would result in a different consideration of the problem.

4. A bowel antigen producing no reactions may indicate the absence of virus or its presence in too small an amount in the material obtained. When the latter is believed to be true, a repetitious attempt is desirable.

5. A satisfactory positive bowel discharge antigen such as Type IB can be used in place of a Frei antigen.

Note: Since this paper went to press, six additional bowel tissue and one vulval tissue antigens were prepared and studied. One was of fresh, unfixed ileitis tissue from a case failing to give any intradermal response to multiple active human Frei antigens. The others were of involved formalin-fixed tissue from cases having given positive Frei reactions: one of the vulva, one of the transverse colon, one of ileo-cecal region, two of the rectum and one of the sigmoid. One, the sigmoid tissue antigen, gave positive intradermal responses in six of ten cases positive to the Frei antigen, and gave no reactions in all of eight cases negative to the Frei antigen. The intradermal inoculations of the remaining antigens gave no reactions in any positive or negative to the Frei antigens. As noted, a positive intradermal response in those giving positive Frei reactions indicates virus presence in the tissue from which the antigen was prepared. The failure to react to such an antigen may not mean such absence.

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DISCUSSION

DR. IRVING GRAY (Brooklyn, N. Y.): Dr. Paulson

is to be congratulated upon his intensive studies in evolving a technic for the practical preparation of a bowel antigen for intradermal use. The skin reaction after intradermal injection of this bowel antigen is analogous to the Frei reaction. Unfortunately little is known concerning skin reaction to virus antigen.

Further experimental work, especially in mice, would seem to be indicated in order to determine whether or not encephalitis can be produced by the use of the bowel antigen. Von Hamm and his co-workers have shown that approximately 15% of the colored population in New Orleans have positive Frei reactions in the absence of clinical Lymphogranuloma Venereum. Dr. Paulson has obtained a few false positive reactions. It would be interesting to know whether these false positive reactions persisted in the same individuals and also how many of the patients were negroes.

Dr. Coca recently informed me that Dr. Arthur W. Grace of the New York Hospital, working with mouse brain antigen, never had a false positive reaction. The mouse brain strain of Dr. Grace has been increasing in virulence so that now the emulsion is diluted 1-40 or 50 in testing rather than the usual 1-10. A papular reaction, excluding the zone of erythema is never less than 7 mm. The normal mouse brain reaction is seldom over 4 mm.; so that the interval between the control and the specific reaction has been widened. The work of Dr. Grace would indicate that false positive reactions do not occur.

I should like to ask Dr. Paulson if he did control skin tests with normal mouse brain?

Has Dr. Paulson ever seen a case of clinical Lymphogranuloma Venereum negative to the Frei test?

Is the use of bowel antigen more specific in the diagnosis than the Frei antigen?

Dr. Paulson has taken a conservative attitude. His intensive and careful studies would indicate that he is dealing with a virus. Whether it is the etiologic agent in the production of ulcerative colitis, in a small group of patients is as yet not conclusive.

Whether this virus is the activating factor or a secondary invader is still a question that must be answered. Definite proof of virus existence must, of course, depend upon its transmission to mice with the production of encephalitis. Once again I want to congratulate Dr. Paulson for his stimulating contribution.

DR. JOHN L. KANTOR (New York, N. Y.): I greatly admire this work and admit that I am no judge of many of the bacteriological details. I should like to ask Dr. Paulson a question. When he says this is a public health menace, what is his conception of the method of spread of the disease? Is it always venereal or has he some other aspect in mind? For those interested in terminology, it may be pointed out that this disease may be called, with equal propriety, either "lymphogranuloma venereum" or "lymphopathia veneria."

DR. ASHER WINKELSTEIN (New York, N. Y.): I think a better term for the disease is indeterminate ulcerative colitis. My impression of the etiology is that a few of the cases are unrecognized amebic colitis and perhaps 20 per cent are chronic bacillary dysentery, and in the rest, the etiology is unknown.

Dr. Paulson's purpose is to point out that a small per cent of those in this remaining indeterminate, 75 per cent are apparently the rectal and colonic types of lymphopathia venereum. Several years ago the idea occurred to me that perhaps some of the female ulcerative colitis patients started in primarily as the Frei disease of the rectum and spread upward. We therefore did Frei tests routinely in a large series of ulcerative colitis cases, first in females and later in males, because males not infrequently get rectal lesions of lymphopathia venereum. The tests were uniformly negative.

We then prepared filtrates of colitis tissue and colitis stools, and tested the skin of colitis patients and of con-

trols in quite a large series. We had over a couple of hundred control patients. In some colitis patients we got a typical skin lesion looking like a positive Frei test. However, we were not convinced by our findings that we had anything definite. It is distinctly possible that Dr. Paulson's work has a broader implication than that some of the cases of ulcerative colitis are lymphopathia venereum of the colon. The broader implication is that it is possible that some or nearly all cases of this 75 per cent "indeterminate" group, are due to another filtrable virus. I think efforts in the future should be devoted to an intensive study of that possibility.

DR. MOSES PAULSON (Baltimore, Md., closing the discussion): Some of the now obvious important implications of this work, just mentioned by Asher Winkelstein, were among the reasons why this study was undertaken. For a long while, I have felt the necessity of another approach in the etiologic studies of the indeterminate enteritides and colitides. My concept that viruses may be factors in some of the obscure digestive disorders resulted in the selection of the virus of lymphogranuloma venereum as

the starting point. It is a virus which gave indications of involving the intestinal tract. I believe that my researches have placed the study and diagnosis of intestinal lymphogranuloma venereum on a more direct and practical basis.

The work points out another approach to digestive diseases in the probability of other viruses living in the alimentary tract possessing possible pathogenic propensities, and has shown a group of cases heretofore designated and treated as indeterminate ulcerative colitis to be associated with—probably caused by the virus of lymphogranuloma venereum.

There is no published record of the purported work at Mount Sinai Hospital in New York City referred to by Asher Winkelstein.

The question of terminology raised by John Kantor has apparently been settled by the editorial staff of the Journal of the American Medical Association who insist upon "lymphogranuloma venereum." His query concerning public health aspects of this virus in relation to bowel antigen, has been discussed in the paper. This is also true of some of the problems brought out by the comprehensive discussion by Irving Gray.

Bacillary Dysentery: Late Results and Relationship to Chronic Ulcerative Colitis*†

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ACCORDING to Hippocrates and Galen (2), dysentery was one of the great scourges of early times. They wrote of the "bloody flux," and down through the ages "diarrhea and dysentery" were of great concern. The medical literature of this country contains pages and pages of data on acute and chronic diarrhea and dysentery which occurred during the Civil War; it also contains the pertinent comment (10) that the "flux caused more sickness and mortality than any other form of disease." Likewise in the Spanish-American War (9) the incidence of dysentery among the American soldiers was 500 per 1,000 soldiers, but the mortality rate was lower, that is, 5 per 1,000, or 1/2 per cent among those who were infected. Hurst and Knott (6) described the ravages of dysentery among British soldiers in the Crimean and other colonial wars; their own experiences with dysentery in the World War led them to consider a probable relationship between chronic bacillary dysentery and what they had previously considered as chronic ulcerative colitis. They quoted Klemperer's similar observations among Austrian soldiers. Of course, the early records of dysentery are confused because of the unknown etiology of most types of the disease. Even the typhoid type was not recognized until the first part of the Nineteenth Century and the Eberthella typhosa was not identified until 1880. Recognition of Endamoeba histolytica in 1875, and the demonstration of Shigella dysenteriae and Shigella paradysenteriae in cases of dysentery in 1898 and 1900, respectively, made it possible to establish some of the different types. The medical records of both the

British and American armies indicate the occurrence of tremendous dysentery epidemics. According to the Medical Department of the U. S. Army (9), the incidence of dysentery in the World War was 0.05 per 1,000 soldiers as compared with an incidence of 494 to 850 per 1,000 soldiers in the Civil War (10). There were 4,546 recorded cases of dysentery or diarrhea of all types among 4,000,000 American troops in the World War and only eighty-five men were discharged because of disability resulting from dysentery (9). This is by no means a true incidence of acute diarrhea, as various medical officers noted that fully 70 per cent of the command suffered from diarrhea but only a few were hospitalized.

The British literature contains many data on this disease and the writings of British authors and the reports of many other writers make frequent mention of chronic dysentery which follows on the heels of an acute infection. We have been unsuccessful in finding any figures which give the incidence of the chronic dysentery which developed from the acute dysentery. Hurst and Knott mentioned the fact that in chronic dysentery, the dysentery bacillus may persist in the stools for months, but that it gradually becomes increasingly difficult to culture it from the feces. The proctoscopic and roentgenologic features of chronic dysentery resemble those of chronic thrombo-ulcerative colitis. Hurst and Knott have long felt that chronic ulcerative colitis is not a disease entity but a later stage of bacillary dysentery. This impression has been affirmed and denied by investigators in many countries. Felsen utilized an opportunity to study an epidemic of bacillary dysentery in 1934. He made a

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follow-up study in 122 cases and found that regional enteritis or chronic ulcerative colitis developed later in 10 per cent.

Kinsella reported that, during the summer of 1921, in various towns of Minnesota, Oklahoma, Indiana and probably in Iowa and South Dakota, there occurred a widespread epidemic of dysentery which was proved to be the result of the Flexner strain of *Shigella paradysenteriae*. Many cases were observed in Rochester, Minnesota, and a group of 140 cases was reported by him, although this group represented only a part of the cases of dysentery that occurred at that time; furthermore, the peak load of summer work limited the opportunities for repeated bacteriologic examination of the stools. He said that in the 140 cases the *Shigella paradysenteriae* (Flexner) was identified in forty-five instances. One cannot conclude that, because a third of a group of patients were suffering from dysentery and were found to be harboring the Flexner strain of *Shigella paradysenteriae*, the remaining two-thirds harbored this same organism. However, Kinsella found no other pathogenic organism in the stools during that period. Because of the technical difficulty of obtaining cultures and the clinical and laboratory load at that time, it is not unreasonable to assume that the cause of diarrhea in all of the cases was the Flexner strain of *Shigella paradysenteriae*.

To judge from various comments, the morbidity of the infection must have been high; "everybody had diarrhea that summer!" There were fifteen deaths in the 140 cases, and fourteen patients came to necropsy. Kinsella obtained positive cultures of *Shigella paradysenteriae* in six cases in which death occurred. In five of the nine cases in which positive cultures were not obtained there was ulceration of the bowel that was characteristic of bacillary dysentery, but in the remaining four cases there was no ulceration. In each instance an attack of acute diarrhea preceded the death of the patient. In three of the six cases in which the cultures were positive the dysentery was a post-operative complication and contributed to the fatal outcome. One child, two and a half years of age, died as a result of dysentery and necropsy revealed a pseudomembranous ileocolitis. In two other cases the post-operative attack of dysentery may have borne some relationship to death. Hence ten of the deaths were in cases in which the dysentery occurred after an operation. In four of the cases in which operation was not performed, the dysentery complicated practically hopeless conditions and was "the last straw." It is obvious that fifteen deaths in 140 cases is not the slightest indication of mortality as there were many more than 140 persons who were suffering from dysentery at that time. It, however, does show that the strain of *Shigella paradysenteriae* was very virulent, and that, in cases in which the patients were infants or elderly persons, or had any serious disease or had become debilitated as a result of a malignant growth, the dysentery precipitated the fatal outcome. It is only repetition to show pathologic specimens, but the appearances of the intestine in some of the cases certainly impress one with the severity of the infection.

A study of the late results of the cases studied by Kinsella has just been completed. It is more than sixteen years since the epidemic; therefore the data are not as complete as one would wish. Fifteen patients died during the epidemic. Twenty-three

patients could not be traced but they apparently were well when they were dismissed. Twenty-four patients died months or years after their dismissal. These patients also apparently were well and had no intestinal symptoms traceable to this epidemic. Seventy-seven patients are known to have lived for one to seventeen years and did not have any intestinal symptoms after their dismissal.

In one case, intestinal symptoms were present until 1929, when they disappeared. Sigmoidoscopic examination in the fall of 1921 revealed what we classified as "early chronic ulcerative colitis" but a roentgenogram of the colon disclosed that the process did not extend beyond the rectosigmoid. For eight years this patient continued to have moderate symptoms and various forms of therapy were administered. In 1925 the diplostreptococcus of thrombo-ulcerative colitis was isolated and a vaccine was prepared. In the eight years the disease persisted, repeated roentgenograms of the colon did not demonstrate extension of the disease beyond the rectum. Oddly enough, after a hysterectomy was performed in 1929 the intestinal symptoms disappeared and in 1938 the patient had not noted any return of the disease. Is this a spontaneous recovery or is it merely a prolonged remission?

Among one of the group in 1921 there was one patient who had ulcerative colitis and who had been under treatment at the clinic for four years prior to the epidemic. During the epidemic she had had an exacerbation of the colitis but this had subsided without causing any serious consequences. This patient died ten years later of pulmonary tuberculosis; no doubt her resistance had been depleted by ulcerative colitis (not tuberculous) which had been present for many years.

We realize that this review, which was made sixteen years after the epidemic, is not comparable to Felsen's careful follow-up study of the 122 cases observed during the Jersey City epidemic. The value of careful intestinal studies in our cases in 1921 was by no means as apparent then as it is now. Likewise, this final paragraph on the Rochester epidemic is merely what we could learn from this particular "sample" and certainly does not permit any generalizations.

We do feel that bacillary dysentery is a widespread disease. With continued improvements in sanitation, the terrific epidemics of the past centuries and even those of more recent years are becoming less and less. If chronic ulcerative disease of the intestine develops only in one of every 100 cases of acute dysentery, the suffering in that one case warrants every possible effort to stamp out dysentery!

From another angle, it is somewhat puzzling to harmonize the world-wide extent of bacillary dysentery with the suggestion that dysentery may be a forerunner of chronic regional enteritis and thrombo-ulcerative colitis. The latter diseases fortunately are not common conditions. Kopelowitz compiled the following figures on the number of cases of ulcerative colitis observed in various hospitals: at the Peter Bent Brigham Hospital, seventy-four cases in twenty years; at the Massachusetts General Hospital, 149 cases in twenty years; at the Mt. Sinai Hospital (including *B. dysenteriae* and amebiasis) 125 cases per year, and at the Cedars of Lebanon Hospital (Los Angeles), thirty-four cases in seven years. A further idea on the relative infrequency of chronic ulcerative colitis is seen in a report by Hurst (5) who noted 288 cases of chronic

ulcerative colitis which have been recorded by seven London hospitals up to 1909; and from 1917 to 1926 (during and after the World War) fifty cases in Guy's Hospital; while in the Birmingham General Hospital he quotes Hardy and Bulmer on ninety-five cases from 1920-1932. Probably the largest series of cases of chronic ulcerative colitis is that of The Mayo Clinic, which consists of approximately 2,500 cases which were observed in thirty years.

For years we have been concerned as to the possible relationship of acute bacillary dysentery to a later condition that we have considered as an entity, namely, "chronic thrombo-ulcerative colitis." Following Hurst's (4) report in 1921, several of our patients who had ulcerative colitis were treated with antidyentery serum under the supervision of Dr. A. H. Logan. The results were discouraging. In 1931, Bagen, Buie and Copeland carried out cultural and agglutination studies for the dysentery group of organisms in fifty-seven consecutive cases of chronic ulcerative colitis but were unable to establish any relationship.

In view of renewed discussion of this problem, and because we felt that a difference in laboratory technic perhaps might have been responsible for our failure to find organisms of the *Shigella* group in these cases, when some of the workers in New York were reporting the presence of these organisms in some cases, Dr. Luther Thompson of the Department of Bacteriology of The Mayo Clinic interviewed Dr. T. T. Mackie in his New York laboratory. He obtained from him his exact technic of making cultures. We were supplied with five strains of dysentery organisms, which in turn had been obtained by Dr. Mackie from Professor E. G. D. Murray of McGill University. Our analysis revealed that three of these strains belonged to the Flexner strain of *Shigella paradysenteriae*, one was a strain of *Shigella dysenteriae*, and another was a Sonne-Duval strain of *Shigella paradysenteriae*. These organisms were used in our agglutination studies. Material for culture was obtained through the sigmoidoscope, and cultures were made immediately following accepted methods, including those of Dr. Mackie. During 1937, thirty-five consecutive cases of chronic ulcerative colitis were studied in this manner. The patients lived in the following places: Ten in Wisconsin, six in New York, three in Nebraska, two each in Michigan, Iowa, Ohio and Kentucky, and one each in New Hampshire, Indiana, Illinois, Montana, South Dakota, North Dakota, Saskatchewan and Alberta. They came to the clinic directly from their homes. In only one instance was an organism of the *Shigella* variety isolated from the ulcers in the rectum and sigmoid colon; this proved to be a *Shigella paradysenteriae* (Flexner). Likewise, there was a high agglutination titre of the serum. No opportunity for study of this case was granted as the patient found it necessary to return home for treatment. It is of some interest that in this case the symptoms of colitis had occurred slowly over a period of seven months.

During the time of this study other cases which we recognized as cases of other varieties of dysentery came under our observation, and the stools or material obtained through the proctoscope, which was cultured in the same way, yielded four strains of organisms of the *Shigella* variety. In these cases the cultures were made in the same manner as the cultures in the cases of chronic ulcerative colitis. In one of these the culture

revealed *Shigella paradysenteriae* (var. sonnei). This culture was obtained in a case of a very severe, destructive ulcerative colonic disease, which was not chronic thrombo-ulcerative colitis. Curiously enough, the patient's serum did not agglutinate the Flexner or Sonne strain of *Shigella paradysenteriae*. Strains of *Shigella dysenteriae* were isolated from three other cases of diarrhea in which there was no ulcerative process in the intestine.

In a few cases of regional enteritis, agglutinating properties of the blood have been tested against these strains of *Shigella*. In two instances cultures of the stool for the *Shigella* were negative but an agglutination titre of the serum in a dilution of 1:320 in one case and 1:160 in the other case, for the Flexner strain of *Shigella paradysenteriae* was noted. A vaccine made from the Flexner strain of *Shigella paradysenteriae* was administered, but the benefit was doubtful. In two cases both cultures and agglutination tests were negative. These few cases are of no significance and do little more than confuse the issue, as we have too few data to hazard any opinion as to etiology of regional enteritis.

SUMMARY

The results in 140 cases of epidemic dysentery were studied. In forty-five of these cases cultures of the stools yielded the *Shigella paradysenteriae* and the cases were reviewed sixteen years after the occurrence of the epidemic. A form of chronic ulcerative colitis developed in only one of the cases. The incidence of intestinal ulceration of a chronic type following large epidemics of dysentery during wars is exceedingly small. Intensive cultural and serologic investigations of the lesions of typical chronic thrombo-ulcerative colitis for organisms of the *Shigella* variety have yielded largely negative results. The results of serologic studies in cases of regional enteritis have been inconclusive in so far as we have data.

As a result of these observations we do not feel that there is sufficient evidence to consider the *Shigella* group of organisms as the cause of chronic thrombo-ulcerative colitis.

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DISCUSSION

DR. T. T. MACKIE (New York, N. Y.): Mr. President and Members and Guests: Dr. Brown has sounded a very much needed note of caution, concerning the potential importance of bacillary dysentery in the subsequent development of some of the chronic diseases of the intestinal tract. There is conflict of opinion concerning the relationship of the *Shigella dysenteriae* to these chronic conditions. It is said by a number of the British workers that about 5

per cent of all cases of bacillary dysentery become chronic and present the morphological and clinical picture of so-called idiopathic ulcerative colitis.

It is also said that the majority of these cases of chronic dysentery result from infection by the Shiga bacillus, and that the Flexner strains are relatively unimportant types, yet this statement is not universally accepted. L. S. Dudgeon, reporting from England, a group of chronic cases developing during the war, found that some 54 per cent followed upon continued infection by the Flexner bacilli.

In this country increasing attention has been focused upon these organisms in the last few years. Some workers maintain that they play a highly important role in the development of chronic intestinal disease. Frequently these diagnoses are based upon the agglutination reaction rather than culture. This method of diagnosis is not above criticism.

We have studied the curves of dysentery agglutinins in a group of patients over a considerable period. The following observations in two cases are characteristic of the group.

Case 1 was studied for forty-two months. This patient had a total of twelve positive cultures for the bacilli from twenty-two attempts which were more or less evenly spaced throughout.

The homologous agglutinin titre at no time rose above a dilution of 1/320, the initial level. Later the homologous agglutinin titre fell to zero, subsequently rising in a brief period again to 1/320. This patient showed a sustained titre of 1/160 for the Sonne bacilli.

The second patient was under observation for twenty-six months. Twenty-nine negative cultures were obtained from the rectal mucosa. The same variability of the agglutinin titre curves was observed. Agglutinins for the Sonne Bacillus reached a dilution of 1/640 on five different determinations, and the curve showed considerable fluctuation. The Flexner titre started at 1/320, dropped to zero, rose to 1/320, fell to 1/160 and again to zero, finally rising to 1/160 up to 1/640. Shiga agglutinins were not present.

Both of these were cases of so-called idiopathic ulcerative colitis.

It has been our experience, therefore, that the agglutination reaction is not a dependable diagnostic procedure. Furthermore, we have been able to demonstrate in the experimental animal the production of dysentery agglutinins by heterologous immunization using strains of *Escherichia coli*.

I wish in closing, to emphasize the necessity for caution in the interpretation of the agglutination reaction in the absence of confirmatory cultures.

DR. BURRILL B. CROHN (New York, N. Y.): It is an old dispute, this question of dysentery. It should be pretty well understood there is a great deal of dysentery throughout the country, as Dr. Brown has said. It should be emphasized that the reports of the Public Health Service of this country show dysentery current through all the states of the country practically all the time, and such centers as Pennsylvania and Massachusetts show dysentery in their states every month of the year and in successive years.

To quote an instance, a case of severe ulcerative colitis seen in Brooklyn, with 104° temperature, diarrhea for several weeks; there was supposedly no contact with any other patient suffering from diarrhea. Nevertheless dysentery was suspected. We found it in the colored maid discharged because of illness, diarrhea; she proved to be a dysentery carrier, and a food carrier in that particular home.

One thinks of dysentery in people returning from the

tropics. I examined a husband and wife just returned from Mexico a few months ago. The husband had diarrhea for two months and had had the typical sigmoidoscopic picture, a definite, subacute proctitis with positive cultures for dysentery bacilli; he was given dysentery serum and antiseptic irrigations before the rectum cleared up.

The British workers found there is a definite form of chronic dysentery. You know that the cities on the Eastern seacoast are repositories for people returning from the tropics, and we have a tremendous population cruising in the West Indies and the tropics; the return of these people by the boatload with diarrhea is a common occurrence. The diarrhea breaks out usually when the boat is three days away from the Coast. (The incubation period of dysentery is about three days). Repeatedly the story is told, "We were well until we were three days out and then everybody in the first cabin was taken with dysentery." It is not generally known that the distribution is not by drinking water or milk, but the British Commission in their work in Syria pretty well proved that the distribution was by flies.

For some time I have thought certain parts of New York City more infected with ulcerative colitis more so than other parts; I thought a survey of the City of New York would prove that there were distributing centers for ulcerative colitis. Contact cases might be suspected, as in my experience I was able to publish two cases of ulcerative colitis in sisters. This is a rare disease and to occur twice in one family was suspicious of a contaminating organism. I reported also regional ileitis in a sister and brother—that is unusual. Both were successfully resected. Such occurrences raise the suspicions of a common bacterial origin for the diseases.

With the assistance of the Board of Health, I was able to plot out the cases of ulcerative colitis in New York. I was disappointed in the chart. I thought I would be able definitely to show there is an area in Brooklyn and there was a small area in East New York where there was a common infecting agent giving rise to chronic ulcerative colitis. Some places in the Bronx impressed me with the idea that there must be some contaminating factor. But when I plotted out the several hundred cases of ulcerative colitis in 1936 in Greater New York, it was obvious that the disease followed the trend of the population and the concentration of the population in the city. There were no specific areas in the city which I could constitute distributing centers.

(Slide used to show result).

DR. PHILIP W. BROWN (Rochester, Minn., closing the discussion): I am grateful to Dr. Mackie and Dr. Crohn for their comments.

The problem, again, has been to me, as I have attended these meetings and worked with these patients over a period of some few years, is that of not defending any particular "belief." I have been impressed by the fact that there is something in the soil of these people that permits this process to go on.

Dr. Crohn has mentioned that he has had an occasional pair that have occurred in one family. In our group of figures that Dr. Borgen presented at the College of Physicians recently, of some 2500 cases of ulcerative colitis, I think there are about twenty or twenty-five pairs, a father and son, a brother and sister, two members of the family that have the disease, but out of that rather large group it is remarkable there are so few that occur in the same family, and it is just the constant reiteration of endeavoring to keep our minds open on this problem and not allowing ourselves to be paralyzed by a "belief"—a "belief" is apparently a rather difficult thing to get around.

Studies of Adenomatous Polypi and Carcinoma of the Colon*

By

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THE problem of the carcinomatous transformation of adenomatous polypi of the colon is of practical and theoretical interest. The occurrence of such a transformation is generally accepted. However, the question as to the frequency of such a development has not been answered unanimously. It would hardly be possible to give due consideration to even a fraction of the literature on the subject. For this reason mention will be made only of the recent investigations of the surgical clinic of Professor Schmieden in Frankfurt and of the pathologic institute of the late Professor Maresch in Vienna because these investigations have dealt exhaustively with the whole complex of problems and have, nevertheless, come to rather opposing conclusions. It seemed, therefore, not amiss to investigate again the question, particularly because there was ample material available for study. Two questions seemed of particular interest: 1. How frequent is the carcinomatous transformation of adenomatous polypi? and, 2. Are there any histologic criteria to recognize those polypi which are likely to become carcinomatous? The same questions have been discussed by the authors previously mentioned. The reason for their divergent conclusions may be attributed in part to the fact that Schmieden and his group studied only surgical material while Maresch and Feyrter investigated only autopsy material.

I had at my disposal a large number of resected specimens, many polypi which had been either biopsied or resected, and sufficient autopsy material. However, for statistical data regarding the frequency of the association of carcinoma and polypi of the colon, 103 resected specimens of the last year only were utilized. This seemed advisable because only within the last year has the necessary careful attention been applied in the examination of the specimens, without which small polypi are so easily overlooked. For the same reason the necropsies of the last 6 months only were used to establish the frequency of polypi in routine autopsy material. Every actual mucosal proliferation was counted even if only a few mm. in diameter. The major part of these polypi was examined histologically. Finally, all the sections of polypi which were submitted for diagnosis within the past ten years, have been re-examined and classified. This material was of greatest value because a considerable number of cases had been followed up for a period of several years. Thus, the histological picture could be correlated with the clinical course.

Investigators who believed in the great frequency of carcinomatous transformation of colonic polypi have based their belief not so much upon a great number of actual observations, but rather upon a seemingly most conspicuous association of colonic carcinoma with polypi. Such association among surgical material seemed the more significant because the only statistic available dealing with the frequency of polypi in

routine autopsy material reported a low percentage of 0.7 per cent only. However, these often quoted figures of Staemmler are evidently incorrect as shown by the recent figures of Feyrter. He found among 1,800 successive autopsies, polypi in 386 cases and a total number of 1,017 polypi because there were several polypi in many cases. The percentage was 21.5 for the total number. If, however, the figures were computed for the decades, the percentage rose in the older age groups to reach 77 per cent at the age of 75 and over.

My total percentage is the same as in Feyrter's observations, but the percentage in the older decades is lower. The percentage of polypi in autopsy material is higher than that found in 103 surgical resections (17.5 per cent). These figures and those quoted by Feyrter approach or even surpass the surprisingly high percentage of 45 per cent polypi found by Schmieden and Westhues in a small series of resected carcinomas. The fact that in unselected autopsy material, polypi are so frequent, especially in the higher age groups, makes it obvious that a frequent association of polypi and carcinoma can not serve as the basis for a computation of the frequency of carcinomatous transformation of polypi. Another source of erroneous frequency figures is the confusion of the situation in diffuse polyposis of the colon with that existing in single or multiple polypi of the colon. The excessive frequency of carcinomatous transformation of the polypi in diffuse polyposis is well established. But there is no reason to identify and confuse this rare, evidently hereditary condition with the most common isolated polypi of the colon.

Actual frequency figures for the carcinomatous transformation of polypi can be calculated if one establishes the actual number of polypi which show carcinomatous transformation and the number of carcinomata which still show the microscopic features of a pre-existing adenomatous polyp. Table I and II shows the figures for the material at my disposal. It is important to note that the routine necropsy material showed a much lower incidence.

Before entering upon the question of the histologic differentiation between harmless and suspicious adenomatous polypi, the distribution of polypi may be shortly evaluated because a supposed predilection of the rectum and sigmoid was accepted as an evidence of a causal relationship between polypi and carcinomata inasmuch as the latter certainly favor the rectum and sigmoid.

A striking predilection for rectum and sigmoid is not evident for polypi as for carcinomata. More than 75 per cent of the latter are found in these parts of the colon, while only 43 per cent of polypi are found in rectum and sigmoid.

The question of histologic criteria for the differentiation between innocent and potentially malignant polypi has occupied the interest of pathologists for many years. Hauser was the first to demonstrate that

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a large number of polypi consisted of glands not identical with the crypts of Lieberkuehn. They were branching and lined by high columnar epithelial cells, not by goblet cells. He regarded these cells as dedifferentiated cells and polypi of this type as potentially

TABLE I

Distribution of polypi in necropsy material

Cecum and Ascending Colon	23
Transverse and Descending Colon	36
Sigmoid and Rectum	44

malignant. Versé in his classical monograph, has taken a similar point of view and has indicated that further cell atypism may be accepted as an evidence of an irreversible cytological change necessarily leading to carcinoma. Schmieden and Westhues have classified colonic polypi according to these cytologic differences and also according to their architecture into three groups. The first type is practically always harmless, while group II and especially III are potentially malignant. This classification is too narrow from a purely descriptive point of view and a good number of polypi can not be properly classified. This holds true for the villous adenomata which form a special group. There are such great variations in the size and shape of the glands, and the type and arrangement of the cell lining that it is hardly possible to give a satisfactory classification.

No single criterion exists which could be accepted as a reliable index for the malignant potentiality of a given polyp. Multilayering of dark rod-shaped nuclei in cylindrical cells or numerous mitotic figures, while always found in polypi which show carcinoma development, can also be detected in polypi incidentally found at autopsy or in instances in which the clinical course indicates the innocence of the lesion. However, the villous adenomas show such a high percentage of malignant transformation that this type should always be looked upon with some suspicion. In general, the frequency with which polypi have been found to be carcinomatous in the clinical polypi studied, warrants their destruction whenever encountered. However, inasmuch as a differentiation between those which are precancerous in a strict sense and those which are innocent can not be made microscopically, conservative treatment must be sufficient. In connection with this

TABLE II

Frequency of carcinomatous transformation of polypi in clinical and autopsy material

Source	Number	Carcinoma	Percentage Carcinoma
Polypi found in colons resected for carcinoma	79	18	22.7
Polypi either biopsied or excised	99	14	14
Polypi found in autopsy material	66	4	6.0

There were actually 122 polypi available for examination. However, 23 found in patients below 20 years were deducted from the total.

recommendation mention must be made of three pedunculated polypi with fully established carcinoma, but without invasion of the pedicle in which resection of the polypi only was done. These patients have been followed for 4 years and are symptom free.

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DISCUSSION

DR. BURRILL B. CROHN (New York, N. Y.): I consider this paper a valuable contribution. If, during a routine sigmoidoscopy, one encounters polypi, my suspicions regarding carcinoma are always aroused. I am a little disabused of that idea by hearing Dr. Klemperer's paper because I realize the wide distribution of polypi throughout the colon, and the common frequency with which they occur.

I note from the tables shown that the increase of polypi is greater with the successive decades; there are many more polypi in the colon in the fifth than in the fourth, and in the sixth than in the fifth, and so forth. I had an idea they were probably all congenital, and that they were all there at birth. Perhaps, there is an inflammatory factor, or a factor of degeneration in the intestinal mucosa; perhaps the increase of polyps in successive decades would possibly account for the greater incidence of carcinoma in the later years.

A word of warning about biopsies during sigmoidoscopies, and this too I learned with Dr. Klemperer: In one case there were two negative biopsies taken from the polyp, yet I had every reason to be suspicious. The third biopsy showed a carcinoma; the resection of the growth showed an advanced malignant degeneration of a polyp. In spite of surgical operation the man died within a few months of widespread metastases.

I should like to warn against negative biopsies in a case clinically suspicious of carcinoma. I have assumed the attitude that negative biopsy or not, if I have a sufficient clinical suspicion, and the appearance through the sigmoidoscope is sufficiently suggestive of carcinoma, I am willing to disregard the negative biopsies and ask a surgeon to resect.

May I ask Dr. Klemperer a question about the incidence of multiple carcinoma in the colon where two or three carcinomas not infrequently take place in one colon, whether there is a relationship between multiple carcinoma and the incidence of polypi? He did not mention the incidence of congenital polyposis. I should like to hear his viewpoint in that regard.

DR. JOHN L. KANTOR (New York, N. Y.): I think we are all very grateful to Dr. Klemperer for such a beautiful presentation. If it is true that you have to section a whole polyp to find one little area of malignancy in it, then it must follow that there is no great use in taking a biopsy specimen since it may obviously miss the malignant area. Therefore, it seems to me that the only thing one can do is to train his eye, his clinical sense, and his clinical judgment, so that he can decide when certain appearances in the proctoscopic picture are sufficiently

suspicious to warrant removal of the polyp. I think it is unfair to lean upon the pathologist. In other words, a thing either looks suspicious or it doesn't, and it is the clinician's responsibility to make the decision.

DR. PAUL KLEMPERER (New York, N. Y., closing the discussion): If I may take up the question as to congenital diffuse polyposis, that is a different problem. These cases, which number, according to the literature, about two hundred, and probably many more which have not been published, show an exceedingly high percentage of carcinomatous transformation. This type of diffuse polyposis should not be confused with the condition of single or few polypi as they are found so frequently at autopsy and also clinically. These cases are commonly familial.

Considerations as regards the frequency of carcinomatous transformation of adenomatous polypi have often been based upon this condition, which is evidently incorrect.

In regard to the biopsy and the necessity of biopsy, I somewhat differ from Dr. Kantor. It is true that the pathologist can not be called to account if he gives a negative diagnosis in a case which later turns out to be carcinoma; nevertheless, in the greater majority of these carcinomatous polypi, as I have shown you here, the diagnosis at biopsy was positive. I wanted only to demonstrate with these specimens that even in a case in which there is a definitely established carcinoma on a polyp, the adeno-

matous areas, which are not yet carcinomatous, do not give any evidence as to the probability that they may become carcinomatous.

I think one should make an attempt to establish the diagnosis by biopsy. The question about which, however, I still puzzle is what to do about the carcinomatous polypi, not the huge ones, which, of course, have to be resected radically, but the smaller pedunculated ones, the size of a cherry and even slightly larger. Is it necessary to resect?

Dr. Crohn quoted one of these cases. I am not quite sure that, when we saw the specimen, it still showed the polypoid appearance. I remember, however, another case where there was no question of the polypoid origin of the carcinoma, the patient dying with metastases after having symptoms for five years or more, but in this case the pedicle was already infiltrated.

I would express the opinion today, though still with reservations, that adenomatous polypi with early carcinoma need not be resected radically, but excision with surrounding mucosa is sufficient.

I hope in a few years to have more material and give more reliable information. Today my material consists only of four cases. These four cases were watched over a period of three and four years, and the patients are perfectly well.

Another point is that polypi that are histologically not carcinoma, and are, therefore, only potential carcinomata can be successfully treated with simple coagulation.

A Study of Gall Bladder Function*

By

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RESULTS obtained with the Graham-Cole gall bladder concentration test do not depend on the function of the gall bladder only, but on a number of other factors.

1. Absorption of dye from the intestine
2. Excretion of dye by the liver
3. Concentration of dye by the gall bladder
4. The effectiveness of the motor meal
 - a. Retention in the stomach
 - b. Absorption in the intestine
 - c. Contraction of the gall bladder and relaxation of the sphincter of Oddi and the duodenum.

Except under rare conditions the time given for intestinal absorption and for hepatic excretion of the dye is sufficient for yielding positive results even when both of these functions should be somewhat impaired. The concentration of the dye by the gall bladder is the function to be tested. To the roentgenologist and physiologist the effectiveness of the motor meal seems to be one of the most difficult technical parts of the gall bladder concentration test. Normally fats delay the emptying of the stomach for many hours. If a fat meal produces nausea, and it does in a number of

cases, then pylorospasm and reversed peristalsis will prolong this delay. The roentgenologists are aware of this and X-ray pictures of the gall bladder are taken for periods of one to three or more hours after the motor meal. When rapid motility of the upper part of the small intestine is present the fat meal is transported into the ileum and its motor effect on the gall bladder is diminished if not abolished. Some patients are allergic against milk, egg, etc.

The mechanism by which fat produces contraction of the gall bladder and relaxation of the sphincter of Oddi is not known. So far Ivy's cholecystokinin seems to offer the most logical clue but unfortunately our preparation have not proven very effective, nor has Ivy as yet produced a pure substance of constant biologic properties. The following work was done therefore in order firstly, to elaborate a simple test on gall bladder function in normal animals, and secondly to find a drug which would make a normal gall bladder empty itself.

Experimental work on the gall bladder has been hampered by lack of simple methods. In man, castor oil, fasting, taking of dye, enemas, a fat meal and the time factor make it nearly impossible to perform a large number of tests on the same individual not to speak of the cost of films and of the uncertainty of obtaining all important phases on the films. In experimental animals on the other hand, technical difficulties

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and cost of films have proven to be preventive to us to test the effect of a large series of drugs on the gall bladder. Acute experiments in which the gall bladder is filled with radio-translucent substances and in which tests are done after the animal awakens from the anesthetic have the disadvantage of abnormal conditions and can hardly be repeated on the same animal. We have therefore developed a simple gall bladder function test in the normal dog similar to the one used by Winkelstein (1) and by Gianturco and Kirklin (2). In an aseptic operation four small lead beads are sewn on the serosa of the gall bladder; 2 on the longitudinal and 2 on the horizontal diameter. Experience in handling of the tissues and the use of papain and citrate solution prevents or minimizes adhesions. The four beads are seen easily with the fluoroscope and are marked on transparent paper. Their distance is measured before and after administration of drugs. The dog is always kept in the same position during each fluoroscopic examination. Control observations without drugs have

variation of 12 hours. No dye is used; no X-ray pictures are taken; no castor oil or enema need be given because the beads are clearly visualized. A number of drugs can be tried in a short time. The new method is simple, rapid and cheap for experimental purposes.

TABLE 1.

The first group of drugs tested belong to the adrenal group. They were chosen because some of them have been described to contract the gall bladder and because some of them were expected to relax the small intestine simultaneously. This was important from the point of view that simultaneous contraction of the gall bladder and of the sphincter of Oddi or duodenum would not permit emptying of the gall bladder. As you can see from the data only adrenalin had a motor effect in that it effectively emptied the gall bladder in most tests. We were not surprised to find that benzedrine sulphate produced a dilatation of the gall bladder because in previous studies we convinced ourselves that administration of this substance evoked

TABLE I
Pharmacology of dog's gall bladder

Drug	Contraction	Dilatation	Indeterminate or no Effect	Drug	Contraction	Dilatation	Indeterminate or no Effect
Adrenalin	7	1	1	Methylguanidin	1	3	6
Ephedrin		2	1	Ergotrate			2
Neo Synephrin	1		3	Ergonovine		3	1
Benzedrine		2	1	Morphine	1	3	2
Benzedrine + Trasentin		1	2	Morphine-Atropine	2		1
				Papaverine	1	1	2
Pitressin	2	1	2	Olive Oil	21		1
Acetylcholine	2X	3	1	Olive Oil Extract	3	1	
Acetylcholine + Adrenaline	1	1		Egg Yolk	4		
Mecholyl	2		3	Milk-Cream	8		
Carbaminoylecholine	1		1	Sodium Nitrite		2	2
Eserin	1	3	2	Atropine		3	
Prostigmine + Acetylcholine	1	2	4	Trasentin		10	1
Pilocarpine			3	Trasentin-Olive Oil-Trasentin	6	11	1
Yohimbin	2	2		Syntropan		2	
Histamine	2		3				

shown that only small rhythmic variations in the size of the gall bladder occur, not exceeding ± 3 mm. A meal of olive oil has been used to test the contractability of the gall bladder. Since in such a meal both diameters contract considerably only such results were termed contractions in which both diameters shortened, and likewise relaxation was assumed to have occurred only if both diameters had lengthened. This was based on the observation that following injection of atropine or diphenyl-acetyl-diethylamino-ethanol-HCL (trasentin),† both of them powerful dilators of the gall bladder, a lengthening of both diameters was observed in practically every case. Only such experiments are reported in which the dogs were in perfect health. The method reported has the advantage that the dogs need no preparation except star-

pylorospasm as well as duodenospasm in man and dog (3). We therefore combined this substance with Trasentin because we expected to obtain relaxation of the duodenum by the latter drug and contraction of the gall bladder by the former. The results did not bear out this assumption. The next group of substances are such that act either on smooth musculature directly or through the vagus nerves. As you see from the table, none of them acted with such regularity as adrenalin. The choline esters produce contraction of the gall bladder and a strong contraction of the duodenum of which we convinced ourselves in acute and chronic experiments. We tried to overcome this with combinations of acetylcholine and adrenalin but without success. In view of recent publications we had expected more clear-cut results from morphine. It makes a great deal of difference, apparently, whether one tests the gall bladder only or the physiological entity

†Generously supplied by the Ciba Company.

of gall bladder, sphincter of Oddi and duodenum. The next group represents the functional controls of our experiments on emptying of the gall bladder, namely the use of substances of which we could expect contraction and dilatation in practically every case. You see the great effectiveness of olive oil, egg yolk and milk and cream. Some simple extracts of olive oil with saline injected intravenously were effective also in contracting the gall bladder but this work is still in the experimental stage. Of the well known antispasmodic drugs of the gall bladder, sodium nitrite and atropine sulphate have been used. A new drug, Trasentin, has been tried also and has been found most effective. This drug had been previously tried in acute experiments in which we convinced ourselves that it had little effect on salivation, on the cardiovascular system and on the pupil; it was found to relax the gall bladder, contracted by barium chloride, pilocarpine, acetylcholine, vagus stimulation, etc. Its relaxing effect on the normal gall bladder of dogs (with beads on the gall bladder) was comparable to that of atropine.

In summary it may be said that with the method described above drugs can be tried easily on normal dogs without dye and without the use of X-ray films. The motor fat meal has been criticized and a number of contracting drugs have been tried among which adrenalin given intramuscularly seems to be the most promising. Among relaxing substances a new synthetic drug, Trasentin, has been found most effective.

LITERATURE

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DISCUSSION

DR. HENRY J. TUMEN (Philadelphia, Pa.): Mr. Chairman, Ladies and Gentlemen: Dr. Necheles has shown a great deal of ingenuity in applying to the gall bladder and the study of its function, this particular method. It is similar in some respects to a method used by Barcroft in the study of splenic contraction and, I believe, by MacSwiney in a study of gastric motility.

The particular virtues of this method are those he already has emphasized, its ease of applicability in the experimental animal, and the fact that it can be repeated without too much expense, and sufficiently frequently to warrant confidence in the results it gives. There is certainly a great deal of need for a method like this because of the confusion that exists about certain phases of gall bladder physiology and pharmacology. One has only to review the literature to see the great deal of confusion that does exist about the use of certain drugs and their action upon the gall bladder, and about certain other problems to which a method like this can be applied, such as the emptying of the gall bladder during pregnancy in animals.

Dr. Necheles has already mentioned the fact that he believes the gall bladder and the sphincter of Oddi and the duodenum must be considered together. The results obtained depend upon the functioning of all three parts of this unit.

It is to be hoped that some of the experiments with drugs will be repeated in such a way that isolated gall bladder action can be determined. Some of the results that Dr. Necheles has mentioned are not in agreement with current conceptions. If we take adrenalin as an example, we find in going over the literature reports such as those of Dale, in which he claims that adrenalin causes contraction of the gall bladder, reports such as those of Westphal, who worked upon rabbits and found that the gall bladder dilates after the use of adrenalin but contracts if

pilocarpine has been used before the adrenalin is used, and reports such as those of Houssay, so widely quoted, in which the gall bladder was found to dilate after adrenalin; and Dr. Necheles' results themselves are not entirely uniform in this respect. I believe he stated that the gall bladder contracted seven times after adrenalin and dilated once and once the result was indeterminate.

I think divergent results such as these are probably due to the fact that there are individual and species variations in the responses to these drugs, and that the tonus of the gall bladder at the time the drug is used probably has some bearing and also that different dosages of the same drug can probably cause different results.

Dr. Necheles feels that the clinical application of this work is in the perfection of some different motor meal for cholecystography. I believe he thinks that adrenalin could be used. We know that there are times when disturbances of the gastro-intestinal tract can cause improper emptying of the gall bladder after the giving of a fat meal; however, that probably does not occur very often and I think it is interesting to observe that Dr. Necheles uses fats as a control for the study of the effect of various drugs and has found a much higher response in contraction of the gall bladder to olive oil than he did to a substance like adrenalin.

It is also true that in patients with gall bladder disturbances, having cardiovascular disease, we might not feel it safe to use adrenalin. I feel, in closing, that there is one question which should be asked, which is not within the scope of the paper to answer, and that is whether or not failure of the gall bladder to empty, after the giving of the motor meal, has much clinical significance. If the gall bladder visualizes normally by cholecystography, and contains no stones, does the fact that it is slow in emptying after a motor meal is given, necessarily mean that the gall bladder can be responsible for the patient's symptoms? Personally, I am not convinced that the question is answered in the affirmative, but I think that a complete survey of that problem is a clinical corollary of any discussion of motor function of the gall bladder.

DR. ANDREW C. IVY (Chicago, Ill.): Mr. President, Ladies and Gentlemen: I should like to ask Dr. Necheles how many drugs he assayed on the same dog during the same day, or what were the periods between the administration of the various drugs to his subject. I raise that point because recently Dr. Doubilet and I have been studying the relation of the pressure in the gall bladder to the response to a threshold or a uniform dose of cholecystokin, and we have found that the pressure in the gall bladder determines the response. This curve (using the blackboard) illustrates our results.

The maximum response is obtained with a pressure in the gall bladder of four and a half to five and a half centimeters of bile pressure. If the pressure in the gall bladder is too low, we either get no response or a slight response. If the pressure in the gall bladder is quite high, we get either a slight response or no response.

This simply means, that optimum tension-length relationship exists in smooth muscle for an optimum response to a standard stimulus. This is true of smooth muscle whether it be in the nictitating membrane, the intestine, or the gall bladder. A distended gall bladder may empty slowly in response to the Boynton meal, because the intra-gall bladder pressure is too high or too low, as well as because of disturbances of the sphincter of Oddi, etc.

So, the point of my question addressed to Dr. Necheles is that if he injected some drug like morphine, which tends to make the gall bladder contract, it might raise the pressure and, if he shortly injects some other drug, the response that he gets to the second drug may be modified by the action of the first drug. In making our studies, we had to permit an hour, sometimes, to elapse between the applications of cholecystokin so as to permit adjustment of the gall bladder.

In regard to cholecystokinin, we can make a good preparation routinely, which is non-toxic in dogs and will make the gall bladder contract and evacuate, but we have not made a preparation which we would recommend for routine use in human beings.

If someone would supply me with a good hard-working organic chemist, I could promise to produce a cholecystokinin which could be injected routinely in human beings, and possibly a good gall bladder function test would be the result, in that we would be applying by intravenous injection, a standard stimulus. Egg yolks and cream by mouth, because of the variable factors pointed out by Dr. Necheles, do not constitute, necessarily, a standard stimulus.

We crystallized secretin recently, and the same can be done for cholecystokinin, with time and the assistance of an organic chemist.

DR. ARTHUR J. ATKINSON (Chicago, Ill.): It isn't surprising that Dr. Necheles in studying the effect of morphine on the gall bladder of dogs obtained results contradictory to those of other observers studying the gall bladder of man. Morphine is a powerful centrally acting emetic in the dog and very small doses produce nausea and vomiting. This central action of morphine will mask and disturb the gall bladder function in the dog.

I should like to ask Dr. Necheles how often he observed vomiting following the use of morphine in the dog.

DR. HEINRICH NECHELES (Chicago, Ill., closing the discussion): One of the reasons why we tried to find a substance that would contract the normal gall bladder was that a number of our patients that were given a milk-cream meal were allergic to milk; in these patients a normal reaction to the motor meal could not be expected.

We are also working on the question whether there may be such a thing as an allergic gall bladder, by adding the offending food to the motor meal; for instance, when we knew that a patient was sensitive to milk, we replaced the milk-cream motor meal by egg yolk or olive oil, and when we then added some milk and cream, we got different reactions.

As to the question of Dr. Tumen, the main thing that strikes me is whether a slow or delayed emptying of the gall bladder following a motor meal means anything. Yet it seems that a number of gall bladders are taken out for

that very reason, and I think this point should be important enough to be considered.

In answer to Dr. Ivy's question, we usually tried only one drug a day, and we did not use the dogs every day, but two or three times a week. We were well aware that a number of drugs produce a condition of the gall bladder which will last for a considerable period of time, e.g., like that following mechohyl. The gall bladders did not respond normally to olive oil afterwards, sometimes for two or three days or for a week.

We have also tried a number of drugs in succession, not to find out the effect of the individual drugs (which we had tried before) but to see whether one drug would influence the other; I have not gone into this because the results were too uncertain, but we took care of this point, of course, in our experiments.

I realize that like in the heart muscle and other musculature, there is a relation between the length and tonus of the muscle fibres and the reaction to drugs or to other stimuli. In our control experiments the diameters of the gall bladder did not vary much, and we are well aware of the importance of this fact.

From Dr. Ivy's publications I had the impression that some preparations of cholecystokinin, contracted the duodenum more, and others less, or not at all.

Dr. Doubilet's question is how completely the gall bladders emptied in our experiments. Of course, we had not observed the gall bladders *in situ*. We don't know whether they collapsed completely. We have given adrenalin intravenously and intramuscularly, and we got contractions of as much as 20 millimeters. Whether that means that the gall bladder folds up, as we frequently see it in acute experiments, I do not know, because we did not want to interfere with normal conditions.

Answering Dr. Atkinson's question as to the effect of morphine, we used doses between five and twenty milligrams which, for the dog are very small and which usually do not produce vomiting. From experiments with apomorphine not reported here, we know that vomiting affects the gall bladder.

I want to end by saying that the main thing I wanted to report today was the use of the new method in the trying out of drugs in what I think are rather ideal experimental conditions.

The Problem of Gall Bladder Infection

By

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THE gall bladder problem has crystallized along three lines of investigation, namely the question of stasis, the study of chemical or metabolic factors and the problem of infection. Many observers believe that the first question centers around or follows the metabolic or infective problems. As interest grows in the various metabolic factors producing alterations in bile, it becomes more and more apparent that an exciting factor must be present. From almost every method of approach the infective problem is the underlying one which demands solution. If that problem is solved, the other problems become more readily understandable.

Several years ago, we presented evidence to show

that chronic cholecystitis, in every way similar to that found in man could be produced in laboratory animals. Since then by varying the technique and by a more difficult method, we have finally attained a point where the evidence is not only complete, in our judgement, but where the associated phenomena are similar to those encountered in the human subject.

Let us briefly review this evidence, craving your indulgence while we review the work which has led to these studies:

1. Testimony from the operating table.

In an attempt to ascertain the incidence of infection we gathered the statistics from over 4395 gall bladders

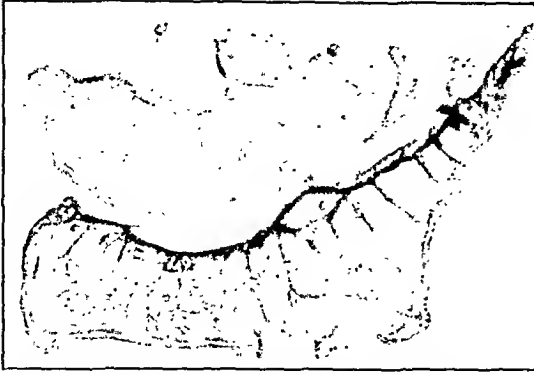


Fig. 1. Type of rare intestinal lesion or colitis produced by antigen No. 7. Upper—normal bowel; lower—diseased bowel.

removed at the operating table, which were submitted to subsequent bacteriological study.

A critical analysis of 2162 cases of gall bladders removed following cholecystectomies, reveals the fact that in about 45% positive cultures were obtained. A little less than one out of every two gall bladders removed on the operating table were infected. The evidence in the remaining group of cases would suggest that a certain proportion of the remaining group had undergone such pathologic changes as one ordinarily associates with transient or even well marked infection at some previous point in the cycle evolving in gall bladder disease. Certainly the destruction of the mucosa, changes in the muscularis and submucosa are those which we have been able to demonstrate in our animals. For that reason, we believe that a bacterial lesion may induce organic changes and in the subsequent periods become entirely sterile. Thereby the conception that bacterial changes in the organ may completely subside or disappear is compatible with some of the pictures encountered in the sterile but incapacitated gall bladder.

The testimony from the operating room is even more important because it incriminates not one organism but a variety of organisms associated with chronic gall bladder disease. These organisms belong to the staphylococci, streptococci, typhoid colon groups and the anaerobic group. There is no single group in which one organism alone is mainly responsible or associated with gall bladder disease. For that reason, we began our work nearly 8 years ago by using bacterial antigens from various sources. These antigens were selected because they were similar to those encountered in the gall bladder on the operating table.

From these studies it was apparent that no one organism was responsible, but that under appropriate conditions. It was possible to reproduce gall bladder disease with antigens varying widely both in their morphological characters and their derivation. Actually, at Frankford Research Laboratory we have used 105 antigens in all and for all sorts of work, nearly 1500 animals. We have been familiar not only with the behavior of the rabbit, which was the animal used, but also with the nature of the lesion produced.

Our present work, which was conducted by Dr. Nelson, was an attempt to improve the methods previously used. Elsewhere, and in detail we hope to consolidate this work which has covered an enormous

amount of material, daily charts, which were kept, followed the condition of each animal. Those of you who are interested can see this data, covering several large volumes recording the progress of each of these animals for the last eight years. Time prevents us from entering into the details of such studies except to point out that only by following such a procedure was it possible to follow these animals from the first stage of inoculation to the final autopsy studies. The early studies consisted in the introduction at measured intervals of small doses of the antigen intravenously. After several series of studies were made, it became apparent that the only successful way in which this work could be carried out was by repeated small injections over very much longer periods of time, capable of inducing, as registered by charts, definite changes in the animal. For this reason, the last series of 109 rabbits represents the nearest approach to a technic which in all probability resembles the disease found in the human subject. This series, received in all 1818 separate injections or 16.6 as the average number given to each animal. The number of injections varied from as low as 2 to as high as 51, the largest number of injections administered to any animal. These animals were observed over many months. Without submitting details, the organism, a nonhemolytic streptococcus from the bowel, produced lesions of the gall bladder in 21% of the first group. In the last series, it produced gall bladder disease in 48 animals or 44% of the entire lot and in 5 further instances the results were doubtful. In other words, by modifying the procedure and adopting a method which more nearly approached the process which may occur in man, we were able to obtain evidence of gall bladder disease in nearly one-half of these animals. These changes were gross and microscopic representing in cross-section practically every form encountered in the human subject, from thickening, swelling, even empyema and perforation. Gross changes in the bile were noted in 40 animals and the cultures were recovered from the bile in 14 of the animals.

These studies illustrate that it is possible to reproduce chronic gall bladder disease in laboratory animals like the rabbit by a bacteriologic antigen from a human source (large bowel). The organism can be recovered and the disease reproduced in similar fashion. This particular strain has gone through a large number of animals, without losing its essential



Fig. 2. Extensive joint lesion produced by antigen No. 7.

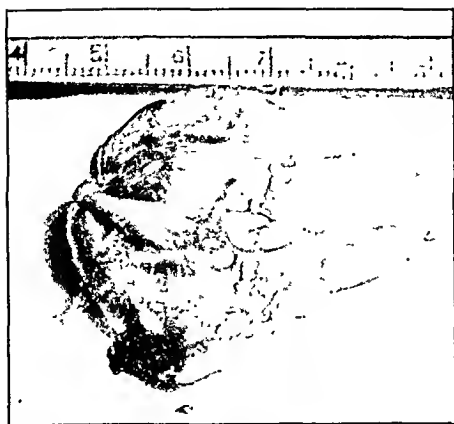


Fig. 3. Valvular heart disease produced by antigen No. 7.

character or its striking power. Furthermore we noted kidney disease, heart disease, and joint disease as the commonest associated lesions. This is interesting because in the experience of one of us 31% of 908 gall bladder histories suggests muscle, nerve, or joint involvement and in 39.6% there was some evidence to suggest impairment of the cardiovascular system. This association is gaining increasing recognition from clinicians. We believe on the basis of our observations that the same etiologic factor which strikes at the gall bladder will affect the kidneys, heart, joint or other organs in the body. Only in this way can we explain the associated disease so often found. We believe furthermore that antecedent infection is essential to gall bladder infection, most frequently in the sinuses, throat and bowel.

The problem of gall bladder infection is therefore first the recognition that chronic cholecystitis can be produced in healthy animals, from strains isolated from the nose, throat, teeth and bowel, etc. In our experience, the most powerful antigen was a bowel strain. For this reason we believe that it is necessary in every case to survey these antecedent or associated foci.

Furthermore there is in the study of a gall bladder problem much which indicates the underlying infectious nature of certain types of this disease. The fact that it is likely to occur after an acute infection, the fact that attacks may follow obvious flare-up of an antecedent or coincident focus of infection in the body and the strong tendency for a certain form of chronic cholecystitis to show seasonal exacerbation, particularly in the spring and fall. All of us who have handled many of these cases recognize the tendency of a certain group to show active signs of inflammation for periods of time. Furthermore in the infectious form there is abundant evidence to show that there are systemic manifestations as well as the local evidence of the disease. Many of these patients are chronically tired, secondary anemia is evident, 31% show some form of rheumatic phenomena, three out of four have a disturbance in colon function, a condition which is conducive to disturbances in the hepato-biliary tract, a vicious circle which the clinician is quick to recognize and which he must control. Associated diseases in the renal, cardiovascular and even endocrine systems is by no means uncommon, aiding in the discomfort of the patient and creating other vicious cycles resulting

in physical inefficiency. The individual with an actively infected gall bladder is usually a tired patient, inclined to insomnia, inclined to fatigue with unmistakable signs of deterioration in physical efficiency.

Physical examination reveals one of the most valuable single clinical signs, namely tenderness over the affected organ. This sign is of vital importance when clearly unilateral and clearly defined over the gall bladder and may supersede all other evidence even when cholecystography and duodenal intubation reveal no evidence in support of such a lesion. We believe no sign is more important than this, but it must be remembered that tenderness over the gall bladder depends upon the position of the organ. As the cholecystographic studies have shown, the organ may be anywhere in the right abdomen and in one case of ours it was in the midaxilla where the tenderness was actually shown to be. Tenderness we believe to be the outstanding sign of the inflamed and, in most cases, the infected gall bladder and disappearance of tenderness, the best single sign of its abatement.

We cannot deny the great values of cholecystography as an aid to diagnosis. It is an objective, anatomic diagnosis, yielding information regarding certain valuable points in the physiological behavior of the organ, but it is far from being a perfect answer to the question of early gall bladder disease. If disease alters the outline or form, interferes with the entrance of the dye, alters its concentrating power or introduces foreign bodies like stone, the evidence of such disease should be available by cholecystographic study. But we are convinced that a normal cholecystogram is comparable with even advanced disease of the gall bladder as we have had occasion to demonstrate. Furthermore by modern reinforcing methods, the interpretation of the quality of the shadow is often difficult. You have, we are sure, seen tender gall bladders which revealed a perfect shadow and we have seen such a gall bladder operated upon which was markedly diseased. For that reason, we believe that such studies must be interpreted with caution and that we must guard against the conception that a normal outline and shadow precludes gall bladder disease. We all know today how frequent are mucosal changes and disease in the gastric wall as revealed by modern endoscopic methods, when X-ray studies apparently revealed a normal organ. We believe that such is often the case in biliary tract disease and, if we had a normal cholecystographic study and a definitely tender gall bladder, we would incline toward the diagnosis of cholecystitis.

From a somewhat different angle, the same criticism extends to the data yielded by duodenal intubation. There is no better method for investigating the physiology of the biliary tract, for detecting alterations in the color sequence and for ascertaining evidence of mucosal disease as shown by the cytology of the bile



Fig. 4. Extensive renal changes produced by antigen No. 7.



Fig. 5. Rather rare hemorrhagic erosions of the stomach produced by antigen No. 7.

fractions. Here again, operative statistics and our own experimental studies show how difficult it is to appraise the bacteriologic evidence afforded by even the most careful segregation. Operative statistics show infection of bile in only 26-28% of cases and even then the organisms were not always similar to those in the gall bladder wall. Furthermore the gall bladder wall may be definitely infected with no evidence of infection in the bile specimens and finally extensive involvement of the mucosa may occur with no evidence by exfoliative data to suggest either the nature or the extent of the underlying lesion. That biliary tract disease does cause in many instances, an alteration of the color sequence, betray its evidences by changes in the cytology of the bile and even convey the organisms responsible for disease is undoubted. But we maintain that gall bladder disease does occur where any or all of these factors are lacking.

We have presented but a short resume of our studies of some eight years, on selected strains and particularly one selective strain. We believe that if other strains were subjected to similar fashions they would probably reveal similar data. With this particular strain we were able to reproduce in laboratory animals chronic lesions in every way similar to those encountered in man. Furthermore we believe that the evidence afforded by a careful clinical study would reveal that infection plays a large role in its evolution.

As we see the problem of chronic cholecystitis, the handling of such a problem depends upon a precise diagnosis. The diagnosis depends upon the history, physical examination, cholecystogram and careful duodenal studies. The history should indicate the extent, duration and type of lesion and it should include a cross-examination regarding the existence of other foci of infection, the control of which is so necessary in this type of case.

The physical examination should ascertain the degree of sensitivity and careful localization of physical phenomena. Again, the physical examination should seek to demonstrate the possibility of any other focus of infection. Infected throats should be bacteriologically surveyed. All teeth should be X-rayed and within the last few years we have cultured duodenal contents, sigmoid smears and catheterized urinary samples. Any antecedent focus of infection should be considered from the standpoint of eradication or control and also

as a source of a possible bacterial antigen. For many years we have used vaccines and filtrates, at times with unusual success. Our method of preparing these vaccines is somewhat different from the accepted routine and most of the filtrates must be markedly diluted. A number of our patients show an allergic skin reaction to various strains of carrier organisms. We prefer not to discuss, in this contribution, the details regarding this type of therapy.

There is no doubt but that the vitamin problem is important for one who is to be put on a diet for a long time. This is particularly the case regarding Vitamins A and D, the fat soluble vitamins and D-1. Active gall bladder patients notoriously show an intolerance for the ordinary preparations of the fat soluble vitamins. They frequently produce regurgitation, flatulence or even active indigestion. For that reason, we have insisted upon the safest of fats, butter fat, and as complete a diet as it is possible for these patients to handle. The building up of the patient requires all those dietetic, hygienic and psychological helps so necessary to the chronic invalid. We can point out, however, from these studies, that the care and control of the colon is a vitally important part of the handling of any gall bladder case. Three out of four cases have colon dysfunction and the question of colon infection is certainly even today, a relatively unexplored field. In a later communication, we hope to give in detail the results of these studies as well as those which have been used in an attempt to control the experimental lesion.

DISCUSSION

DR. WILLIAM A. SWALM (Philadelphia, Pa.): I should like to ask Dr. Rehfuess one question. We have been very much interested in the etiology of cholecystitis. He has had a marvelous opportunity here of saying whether he believes the infection might in a majority of the cases be mucosal in origin, submucosal, with its rich vascular network, or serosal. Of course, the muscle, I suppose, is unimportant in the majority of the cases. If he caught them early enough, did he open up the gross specimens and try to study that point?

DR. IRVING GRAY, (Brooklyn, N. Y.): The authors are to be congratulated upon their intensive studies. During the past year Dr. Walzer and I working with the Macacus Rhesus monkey, have demonstrated that antigen is absorbed from the gall bladder. We have sensitized the skin and the mucous membrane of the intestinal tract in the rhesus monkey by means of passive transfer. Several days later the specific antigen was introduced into the gall bladder. Within a short time (approximately five minutes) a local allergic reaction developed at the sensitized sites. We have also sensitized the mucous membrane of the gall



Fig. 6. Extensive chronic cholecystitis produced by antigen No. 7.



Fig. 7. Extensive mucosal changes in chronic cholecystitis produced with antigen No. 7.

bladder by passive transfer and a few days later introduced the antigen intravenously. There developed at the sensitized site in the gall bladder a local allergic reaction. The changes in the mucous membrane were similar to those which occurred in the mucous membrane of the ileum and colon of the human being. Moving pictures of the allergic reaction as it occurs in the mucous membrane of the gastro-intestinal tract in humans were shown before this association last year.

I should like to ask Dr. Rehfuss, whether he has any method or means of determining if the changes that occurred in the heart, in the joints and in the kidneys of the rabbits which he studies were due to the absorption of antigenic substance from the infected gall bladder. If it could be shown that the injection of streptococci first produced cholecystitis in the rabbits and that changes subsequently occurred in the other organs, one could reasonably assume that antigen was absorbed from the diseased gall bladder.

Our experimental studies on the rhesus monkey indicate that not only can the gall bladder be the seat of an allergic reaction but also that antigen is absorbed from this organ.

DR. HEINRICH NECHELES, (Chicago, Ill.): In connection with the work that I reported, I should like to make a suggestion to the speaker. In the rabbit and the dog, Dakin's solution given intravenously in small doses, is known to produce a slight cholecystitis. We are doing this in our experimental animals and then are trying the response of the various drugs tested on the normal gall bladder. It is an old question whether an infection of the gall bladder begins in a normal or in a damaged organ.

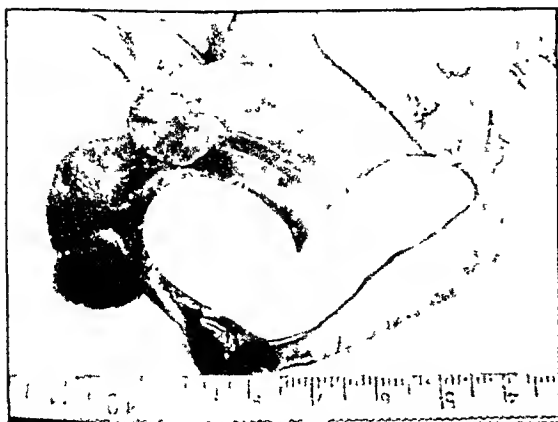


Fig. 8. Empyema of the gall bladder produced with antigen No. 7.



Fig. 9. Cross-section typical case of chronic cholecystitis showing involvement of all the walls.

The use of Dakin's solution, of course, is rather crude experimental technique, but one may possibly be able to simulate disturbances of the gall bladder produced by changes in adjacent organs. By making the gall bladder a focus of lessened resistance a greater percentage of "takes" may be produced when bacteria are injected into these animals.

DR. MARTIN E. REHFUSS (Philadelphia, Pa., closing the discussion): The best way I can answer these things—I should like to answer them in turn, but I will begin with Dr. Boyd's remarks. He reported the experiments of Wilkie and other experimenters. In the first place, this is chronic cholecystitis, not acute cholecystitis. This lesion has taken over two years, in some instances, to produce. How much does a man need to prove chronic cholecystitis? Where do you get the muscle thickening? I have shown only a few slides because I couldn't show all I wanted. How much information and evidence does he need to be satisfied? One of these experimental gall bladders is ten and twelve times the normal thickness. This is not acute cholecystitis that the experimenters have been talking about. We went through that. I saw the work in Rochester and went carefully over Wilkie's work, but the only way to do this is to do what we did, and when somebody spends five years, as Nelson and I have done all together, working day after day, and produces this sort of thing, or fails to produce it, I will believe the sort of testimony they may bring.

I, for one, am absolutely convinced. We selected the rabbit because we are familiar with it. The dog wasn't selected because we couldn't use the dog. Even with our space we couldn't manage it from a practical angle.

Now the question comes up, as Dr. Swalm has mentioned, the questioned of the etiology of gall bladder disease. When he speaks of etiology, I presume the cause of it—he means what way has this particular type of thing come about. When I am talking about chronic cholecystitis, I can talk only of the particular antigen we have used.

Streptococcus viridans and some other strains do hit the gall bladder and others do not. The same thing is true regarding the hemolytic group. In this particular strain I can show slides showing every part of the gall bladder wall involved, the mucosa, the submucosa, and muscularis, and I should be glad to demonstrate others if he will come out to the laboratory.

Regarding the other questions, the point is, here is a culture in an animal, the production of a disease, the obtaining of a culture again, and the reproduction long enough to be reasonably certain these things go together; and the other striking thing is that this antigen not only hits the gall bladder but also other organs, particularly the joints, and the heart, and kidneys. Clinicians are waking up to the fact that chronic gall bladder disease is frequently associated with cardiovascular or nerve and muscular disease.

In the cases I diagnosed in eight years, they had nerve, muscle, or joint involvement in some part of their history, in 31% of cases and some did have active arthritis. That is what these animals do under similar circumstances.

Thirty-nine per cent of our patients with chronic gall bladder disease had some sort of heart consciousness, and they are beginning to talk of the association. Here is the only place I am going to speculate. We believe that the same underlying etiologic factor hits both places at once, not the gall bladder first, and heart and vascular system later, but probably all these things at one time, and there is a shift in relationship. We see that shift definitely in animals. We stop our injections and the phenomena clear up. Again we find gall bladders that have no definite bacteria but have been damaged.

Someone said, "How about the human gall bladder?" Well, study the literature and find out whether it has been cultured; secondly, whether the culture was introduced into animals, and you will find the evidence in the literature is very incomplete. Some men give every detail and others simple, sparse information as to the finding of bacteria, but there are at least two thousand cases in the literature where it has been worked out very carefully, and in those two thousand cases, only 45 per cent, were found infected.

How about the sterile gall bladders on the operating table? The pathologist reports damage to the mucosa and reports changes in the submucosa and muscularis. Where did the changes come from? Did they come from metabolic disturbances, I ask you. Perhaps they did. Perhaps it is possible with Dakin's solution, but neither you nor I have ever taken enough of it to guarantee we will get a cholecystitis. In closing, the fact that you don't get a culture on the operating table is no evidence whatsoever that there hasn't been an antecedent infection. When we inject our animals and stop, the antecedent infection disappears, but the damage is there; therefore, if I may have digressed, I have been doing a great deal of thinking on this subject and until we can strike at the underlying factors that have induced the changes in the gall bladder, I do not believe we can make much progress. I believe it is your business and my business, as internists to work out a combination of affairs which will cause subsidence of gall bladder infection, and I am one of those who believes that it does take place.

The Relationship of Lesions of the Cystic Duct to Gall Bladder Disease*

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ALTHOUGH attention was called to the relationship of lesions of the cystic duct to cholecystic disease many years ago by Schmieden and Rhode (1), Seelig (2) and others, this feature of cholecystic disease, particularly partial obstruction of the duct, in the absence of stones has received very little attention since then. During the past few years the author has observed numerous patients with typical history of gall bladder disease who were cured following cholecystectomy although very little evidence of inflammation was noted in the body of the gall bladder. This is, as a matter of fact, an old observation. Many of these gall bladders contained no stones. The lack of correlation between symptoms and the amount of pathologic change in the gall bladder has been generally recognized for decades. While conducting a study of this relationship, the authors noted that not infrequently the fundus showed very little, if any evidence of disease, but sufficient pathologic change was noted in the cystic duct to explain the symptoms. Most of these lesions encountered were of the type which would lead to obstruction of

the duct particularly if a local temporary disease would induce edema at that point. The absence of severe pathologic change in the wall of the gall bladder would lead one to suspect the possible presence of Westphal's (3) biliary dyskinesia as popularized in this country by Ivy (4), Walters (5), Best (6) and others. Unfortunately the gross appearance of the fundus of the gall bladder may be similar (i.e. frequently almost normal) in biliary dyskinesia and obstruction of the cystic duct. Differentiation then could only be made by examination of the duct. Many of the cystic duct lesions will not be discovered until after cholecystectomy when the duct can be opened. If the symptoms are caused by lesions of the cystic duct cholecystectomy will relieve the patient, whereas in at least one of the types of biliary dyskinesia, removal of the gall bladder is apt not to alleviate the symptoms.

ANATOMY AND EFFECT OF PATHOLOGIC PROCESSES ON THE PHYSIOLOGY OF THE CYSTIC DUCT

There is probably no organ in the body which is so subject to variations or anomalies as is the cystic duct.

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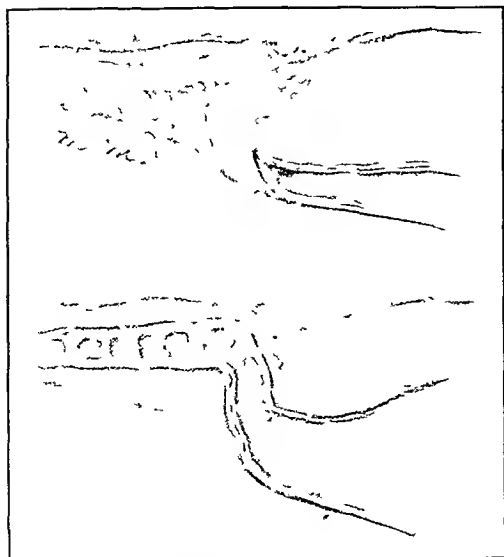


Fig. 1 Drawing showing cystic duct (before and after opening) after cholecystectomy in Case 4. Cholecystogram revealed no shadow. There is an angulation of the cystic duct with a marked fibrosis of its wall as shown in Fig. 2.

These variations include all features such as size, length, shape, etc. Although it is usually stated that the cystic duct is "S" shaped, Mentzer (7) found that in a study of 612 autopsy cases this shape was noted only in 19. In 41 instances the duct was curved rather sharply and flexed upon itself. It is agreed however that the duct is not a direct continuation of the neck of the gall bladder, but leaves from the side. Variations in the cystic duct with particular consideration of the valves of Heister have been very ably discussed recently by Lichtenstein and Ivy (8). Most anatomy books describe the valves of Heister as being arranged in a spiral fashion down the lumen of the cystic duct, but in our study of pathologic gall bladders as removed at operation, very seldom indeed was a duct encountered with spiral valves. Whether or not the loss of the spiral shape of the valves per se has anything to do with gall bladder disease is a question which the present study does not answer. However, certain anomalies as will be described do appear to have a definite relationship to cholecystitis. Experiments performed by Lohner (9) suggested that the valves impeded the flow of fluid from the gall bladder to the common duct more than the flow in the reverse direction. However, Johnson and Brown (10), Mentzer (7) and Lichtenstein and Ivy (8) were unable to demonstrate any significant difference in the pressure required to force fluid through the duct in the two directions. The latter authors concluded that the function of the valves is to prevent distension or collapse of the cystic duct in case sudden pressure changes occurred in the gall bladder or common duct.

The wall of the cystic duct is composed of three layers of smooth muscle fibers similar to the gall bladder. A few authorities are of the opinion that there is actually a sphincteric action at the upper portion of the cystic duct and that a spasm of this region, with consequent obstruction to proper flow of bile, might exist under pathologic circumstances. At the present time however there is insufficient evidence available to

support the theory that an actual spasm with sufficient action to produce obstruction could exist. The acute bend of the neck of the gall bladder and a fold of the mucous membrane which is frequently present at that point may at times act in an artificial way as a sphincter.

PATHOGENESIS AND RELATIONSHIP OF CYSTIC DUCT LESIONS TO SYMPTOMS

It is generally agreed that normal Heister valves do not offer significant obstruction to the flow of bile either into or out of the gall bladder. When congenital or inflammatory lesions constrict or impinge upon the lumen of the duct it is obvious that a certain amount of obstruction will be produced, particularly when the impingement on the lumen is increased by attacks of acute inflammation which might involve that area. It is well known that acute or subacute inflammation occurs about the gall bladder in attacks varying greatly in frequency and intensity. Obviously if the obstruction is complete and extends over a period of days or weeks hydrops or empyema will result. An important feature in the clinical significance of lesions of the cystic duct lies in the fact that many of them are congenital, representing anomalies of the cystic duct or valves of Heister, and produce no symptoms until late adult life when inflammatory processes are known to be most prone to manifest themselves. Edema at the point in question (e.g. kink in the duct, or transverse fold of Heister) will then produce significant obstruction which may or may not be complete. This edema might subside rapidly, but if the inflammation



Fig. 2. Photomicrograph of section of wall of cystic duct in Case 4. The wall is greatly thickened and the muscle is almost completely replaced by fibrous tissue. Since the body of the gall bladder was so slightly diseased it appears that the explanation of the failure to obtain a shadow on cholecystogram lies in the obstruction produced by thickening of the cystic duct and the angulation.



Fig. 3 Enlarged photograph of the cystic duct in Case 3. Note the maze of fibrous strands located in the neighborhood of the folds of Heister. These strands are probably congenital and inflammatory in origin, and represent the only explanation found of the patient's symptoms which were so typical of gall bladder disease. This maze of fibrous strands possibly acted as an obstruction to emptying of the gall bladder shadow as shown in Fig. 4. The most scarring and obstruction is noted at the distal end of the duct.

was sufficient to produce ulceration the resultant scar might be sufficient to produce a partial obstruction even without the aid of subsequent inflammation with its incident edema. Recent theories regarding the etiology of gall stones indicate that a certain group (particularly cholesterol) may form in the gall bladder, because of abnormal metabolic factors in the absence of any disease of the gall bladder itself. Any of these stones when small might produce edema and ulceration of the cystic duct while passing down the duct and be the primary cause of ulceration and scar formation. It must be remembered that an acute inflammation may develop in a previously normal duct and likewise be responsible for the development of scar and adhesions.

It is obvious that if the obstruction of the cystic duct is present in a gall bladder whose wall is sufficiently normal to concentrate bile, the obstruction will be more apparent because the bile will be much more viscid and pass through the obstructed area less readily than hepatic bile. As a matter of fact, the pain in the patients in this series was perhaps most acute in the group of patients whose gall bladders responded with normal density in cholecystograms, but in which emptying was delayed as demonstrated by response of

the gall bladder shadow to the fat meal. Since various factors such as adhesions, scar formation and stones are known to produce complete obstruction, it appears quite logical to assume that a partial obstruction would likewise be common, and perhaps even more common than complete obstruction. Since it is known that partial or complete obstruction of the lumens of other communicating channels in the human body occur rather frequently, is it illogical to conclude that the cystic duct may be similarly involved? It is extremely difficult to prove by experimental methods that partial obstruction of the cystic duct exists to any significant extent because after the gall bladder is removed, the relationship of the pathologic lesion to its points of fixation, etc., are totally destroyed thereby invalidating the results. Tests performed with the gall bladder *in situ* before removal of the organ might yield informative results but such procedures would be time consuming and be difficult to justify while the patient was under an anesthetic. It is a well known fact that when the gall bladder is straightened out emptying of the organ is greatly facilitated. Adhesions which are so prevalent about the cystic duct would almost of necessity interfere with straightening of the gall bladder even with the most striking muscular effort, and in that way alone interfere with emptying.

In 1927, Lyon and Swalm (11) called attention to edema of the cystic duct as a factor in obstruction of the duct and production of symptoms designated as cholecystic in origin. They spoke of this condition as catarrhal inflammation and recognized the fact that after the inflammation had subsided normal function of the gall bladder, as determined by cholecystography, might be regained. For this reason surgery must be advised much more cautiously in this type of lesion. It would appear that acute inflammation of the cystic duct would be a frequent lesion, particularly since the lymphatics from the various abdominal organs pass so near the duct and frequently are contiguous with it. The frequent presence of dense adhesions about the cystic duct supports this contention. It cannot be determined how frequently inflammation in the cystic duct spreads to the body of the gall bladder or vice versa. Experiments are being started in this laboratory in an endeavor to obtain information on this point. It is likewise difficult to determine through which anatomical structure (i. e. mucosa or serosa) the inflammation might spread. Evidence is already available, however, to indicate that chronic obstruction of the cystic duct may result in pathologic processes on the gall bladder side. Phemister and associates (12) have called attention to the development of calcium stones and calcification of the gall bladder wall in the presence of chronic obstruction of the cystic duct. It is obvious that an obstruction of the cystic duct, though incomplete, would result in stasis. Many authorities consider that this is an important factor in the development of gall bladder disease including the development of stones (Naunyn, Asehoff and Baemeister). It is possible that partial obstruction, particularly when temporary, may be associated with a more extended effort on the part of the gall bladder to empty itself. Whether or not this increased activity has anything to do with the production of pain cannot be determined decisively.

Up to the present time there is no unanimity of opinion as to what pathologic factor is responsible for the various symptoms observed in cholecystitis.

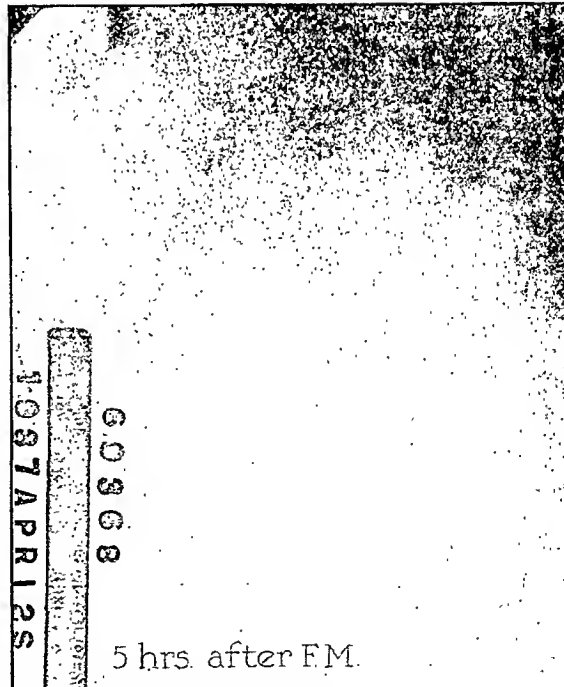
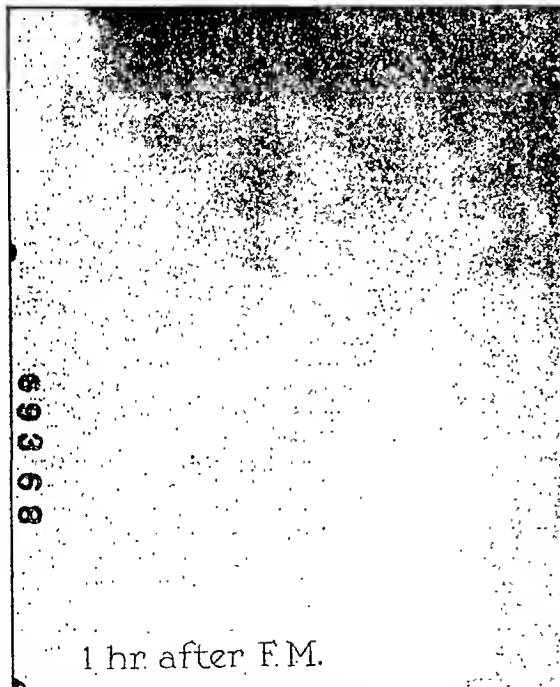
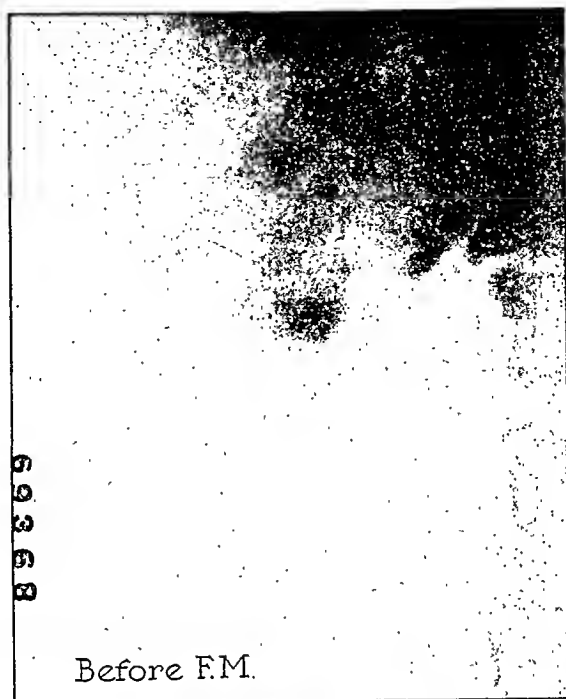


Fig. 4. Cholecystogram showing response of the shadow to the fat meal. There is such a delay in emptying of the gall bladder that a dense shadow still remains 5 hours after the fat meal.

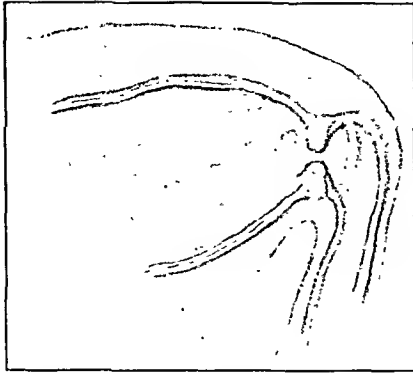


Fig. 5. Drawing of the cystic duct in Case 6. A large fibrotic nodule was found at the location of the 1st fold of Heister, and probably represents a lesion implanted on it. This lesion was not annular, and for that reason probably did not act as a very significant obstruction. Cholecystogram showed no shadow. There was moderate thickening of the gall bladder wall, and stones were found in the gall bladder and common duct. (See Fig. 6).

Certain features are apparent however. For example, when a stone becomes lodged in the cystic duct or is being passed through the cystic duct or common duct, the pain which is so typical of gall bladder disease is reproduced. It is equally well known that a patient may carry stones in the gall bladder for years without the presence of any pain whatsoever. Although more difficult to prove, it appears that if stones in the common duct remain in the duct without approaching and blocking the sphincter of Oddi, pain may be very insignificant. It is probable that infection of the gall bladder wall itself does not produce severe pain—particularly of the colicky type. The fact that cholecystogastrotomy or cholecystoduodenostomy, which is usually associated with considerable infection of the gall bladder wall and liver (Lehman, Horsely and others), is rarely associated with pain in the right upper quadrant, (though may be associated with dyspepsia) supports the contention that the severe pain in gall bladder disease arises from a site other than the gall bladder wall. Lichtenstein and Ivy (8), Womack (13) and others have called attention to the presence of numerous nerve fibers and ganglia in and about the cystic duct, implying that lesions in this area might be painful. Obviously, the mere presence of numerous nerve fibers here does not prove that the cystic duct is a particularly sensitive spot but clinical experience supports this assumption in so far as it is well known that during the early stage of obstruction of the cystic duct by stone, the condition is commonly accompanied by severe gall bladder colic.

CLASSIFICATION OF OBSTRUCTIVE LESIONS OF THE CYSTIC DUCT

Complete obstruction of the cystic duct leads to hydrops or empyema of the gall bladder. These two conditions are frequent and are so well known that they will not be discussed here. However, we wish to call attention to the fact that in many instances no stones will be found in the ducts of patients with hydrops and empyema, indicating that the stenosis was presumably produced by scar resulting from an inflammatory process. The incidence of non-calculous lesions in incomplete obstruction of the cystic duct

will be much higher than in complete obstruction (i. e. hydrops and empyema) because the stone acting as a foreign body, would tend to increase the inflammatory process to a maximum.

The lesions capable of producing an incomplete obstruction of the cystic duct are numerous indeed. Most of them as listed below have been mentioned at various times in the medical literature by various authors. Generally speaking lesions of the cystic duct may be congenital or inflammatory in origin (rarely neoplastic) and may be secondary to changes in the wall itself or in the valves of Heister.

LESIONS RESPONSIBLE FOR OBSTRUCTION (PARTIAL OR TEMPORARILY COMPLETE) OF THE CYSTIC DUCT

1. Stenosis produced by surrounding adhesions. (Case 1)
2. Stenosis produced by a thickened wall.
 - (a) Due to acute inflammation.
 - (b) Due to diffuse fibrosis. (Case 4)
3. Congenital or inflammatory twists or kinks. (Case 2)
4. Congenital or inflammatory lesions involving valves of Heister.
 - (a) Fibrous strands. (Case 3)
 - (b) Local deposition (nodules) of fibrous tissue. (Case 6)
 - (c) Stricture due to scar.
 - (d) Valve-like anomalies. (Case 5)
5. Stone in the duct. (Case 7)
6. Tension induced by enlarged liver.
7. Compression or filling defect due to tumor or lymph nodes.
8. Obstruction due to anomalous hepatic or cystic artery.

1. *Stenosis produced by surrounding adhesions.* This is perhaps encountered more frequently than any other lesion. By no means are all of them obstructive in spite of the fact that the duct may be buried in adhesions. This group is illustrated by Case 1, a woman who had a cholecystostomy one year previously with recurrence of symptoms after a few months. The cystic duct was buried in dense adhesions and was so small that it is difficult to see how bile, particularly viscid bile produced by a gall bladder with normal concentrating ability, as was present in this patient (see Fig. 8) could pass through the compressed duct.

2. *Stenosis produced by a thickened wall.* The wall of the cystic duct may become thickened by acute inflammation (i. e. edema, etc.) or by the deposition of fibrous tissue. Obviously the acute inflammatory process would be observed only when cholecystectomy has been performed for acute cholecystitis. If such an acute process were severe or recurred numerous times it is to be expected that an unusual amount of fibrous tissue would be deposited. This is what was found in Case 4 (see Figs. 1 and 2). This patient had severe pain in the right upper quadrant of 5 years duration. Cholecystogram showed no shadow. At operation the duct was rather sharply angulated, small, and its wall thickened. The thickened wall made the lumen very small indeed. The wall of the gall bladder in this patient was only very slightly diseased, implying that the stenosis of the cystic duct produced by the thickened wall may have prevented the entrance of sufficient bile into the gall bladder to allow the de-

velopment of a shadow on the cholecystogram even though the gall bladder itself may have been able to concentrate bile.

3. *Congenital or inflammatory twists or kinks.* Twists and kinks are quite commonly encountered at the operating table but seldom will one be able to differentiate between a congenital and inflammatory lesion. The presence of dense adhesions may point to an inflammatory origin but obviously the twist or kink may have been present before the adhesions were deposited and in fact may have been an important factor in the pathogenesis of the inflammation which resulted in the adhesions. The lesion is illustrated by Case 2, a woman having had a cholecystostomy performed twelve years previously. Attacks of pain in the right upper quadrant recurred after six years. The cholecystogram, as will be discussed later, revealed a shadow of normal density but was deformed and emptied only slightly after the fat meal. Operation revealed a few adhesions attached to the gall bladder, presumably resulting from the previous operation, but the wall was only very slightly diseased. The duct was sharply angulated and buried in dense adhesions. Here again it would appear that the stenosis of the lumen (as produced by the kink) was sufficient to interfere with the emptying of viscid bile which was presumably produced by her gall bladder as suggested by the cholecystographic shadow of normal density.

4. *Congenital or inflammatory lesions involving the valves of Heister.* In this group may be included obstructive lesions produced by fibrous strands, local

nodules consisting of connective tissue, stricture due to scar and valve-like anomalies. These may be congenital or inflammatory except that the latter group is most apt to be strictly anomalous.

Case 3, who was a woman complaining for fifteen years of pain in the right upper quadrant radiating to the back, had a gall bladder with a cystic duct obviously partially obstructed by numerous fibrous strands. (See Fig. 3). The cholecystogram revealed a gall bladder shadow of normal density but it failed to empty after a fat meal. (See Fig. 4). As might be expected the body of the gall bladder appeared practically normal grossly and microscopically. The maze of fibrous strands which are no doubt associated with the folds of Heister are so numerous that it is difficult to understand how bile could pass, particularly viscid bile from the gall bladder which was obviously still able to concentrate.

The gall bladder of Case 6, who had been complaining of severe attacks of pain in the right upper quadrant of four years' duration, had a large solitary nodule $\frac{1}{2}$ cm. in diameter located at the junction of the cystic duct and neck of the gall bladder at about the location of the first fold of Heister. (See Fig. 5). This nodule was composed solely of scar tissue, as shown in Fig. 6. The lumen of the duct was open sufficiently to suggest that the nodule would be obstructive only in the presence of edema incident to inflammation. Cholecystogram revealed no shadow. At operation stones were found in the gall bladder and common duct. The gall

Protocol of cases Illustrating partial obstruction of the cystic duct*

Case No.	Sex Age	History	Type of Pain	Cholecystogram	Op. and Path. Findings		
					Body of G.B.	Cystic Duct	Stones
1 A. F.	F 46	C'stomy 1 yr. ago. Relief 6 mos. Frequent attacks pain typical G. B. disease.	Usually colicky. Very little dyspepsia between attacks.	Norm. density. Very little resp. to F.M. Dense but smaller shadow after 3 hrs.	Slightly thickened. Few adhesions.	Stenosed. Buried in dense adhesions.	No
2 A. D.	F 38	C'stomy 12 yrs. ago. Relief 6 yrs. Recurring attacks pain R.U.Q. with lot vomiting.	Usually occurred as attacks of colic typical of G.B. disease.	Norm. density. Deformed. No evidence of emptying 1 hr. after F.M.	Wall about normal. Few adhesions previous op.	Sharply angulated. Buried in dense adhesions.	No
3 E. B.	F 46	Pain R.U.Q. 15 yrs. duration radiating to back. Vomiting frequent. Aversion to fatty food.	Severe. Radiates to back. Mild colic.	Norm. density. Still dense shadow 5 hrs. after F.M. (See Fig. 4).	Appearance about normal.	Fibrous strands (V. Heister) obstructing lumen (See Fig. 3).	No
4 S. W.	M 47	Disabling symptoms typical of G.B. disease. 5 yrs. dur. Jaundice 2 mos. shortly after onset.	Very severe and quite constant. Few attacks colic.	No shadow.	Few filmy adhesions. Wall gray, not thickened.	Buried in adhesions; angulated; wall thickened (See Fig. 2).	No
5 N. R.	M 37	Severe attack pain with vomiting 3 mos. ago. Dur. 6 days. Dyspepsia since. Fatty food reproduces pain.	Rather constant. Occasionally colicky.	No shadow.	Slight thickening.	Valve-like cuff at opening of cystic duct.	No
6 E. B.	F 37	Severe symptoms typical G.B. disease 4 yrs. dur. 2 short attacks jaundice.	Colicky. Occurred in attacks. Mild dyspepsia.	No shadow.	Moderate thickening.	Large fibrotic nodule at site 1st Heister fold. (See Fig. 5).	In G.B. and C.D.
7 C. S.	F 37	Frequent attacks severe pain R.U.Q. with nausea and vomiting 5 mos. dur. 1 attack jaundice at onset.	Severe colic in R.U.Q. occurring in attacks.	No shadow.	Normal fundus. Numerous small stones.	Stone encysted in cystic duct.	In G.B.

*All of the patients were relieved of symptoms by cholecystectomy, but were operated so recently that the permanency of cure cannot be determined. Case No. 3 was relieved of pain in the right upper quadrant but has gained about 50 lbs., and is now complaining of pain in the lumbo-sacral region and cardiac region.



Fig. 6. Microscopical section of the nodule projecting into the lumen as shown in Fig. 5. The lesion consists of connective tissue (C) in which a few muscle bundles (M) are interspersed, and appears to be the residue of an ulcerative process, possibly associated with the gall stones. In support of this assumption is the fact that the scar is densest at the mucosal side near the lumen.

bladder wall was diseased sufficiently to cast doubt as to the ability of the organ to concentrate, thereby making it difficult to tell whether the lack of shadow on cholecystogram was caused by an obstruction of the cystic duct or by disease of the gall bladder wall.

Strictures due to scar formation are undoubtedly common and probably account for the great majority of cases of hydrops or empyema of the gall bladder in which no stones are found.

Valve-like anomalies are probably congenital in origin and are quite frequent. Originally they were apparently large folds of Heister but became cup shaped because of the pressure exerted by viscid bile and concretions or stones from the gall bladder side. The fact that their concavity practically always faces the gall bladder suggests that they have acted as an obstruction to the contents of the gall bladder while being expelled through the duct. Case 5, a man aged 37, with pain of only three months duration, had a large well formed cup shaped valve-like fold at the junction of the cystic duct and neck of the gall bladder where the lumen was still 6 to 8 mm. in diameter. When filled this cup shaped fold, which extended all the way across the duct undoubtedly acted as a serious obstruction. Obviously, when collapsed, bile could enter the gall bladder without difficulty. If edematous it would obviously produce an obstruction in both di-

rections. Cholecystogram revealed no shadow, but it was performed a few days after an acute attack of right upper quadrant pain. Unfortunately, we did not get a later cholecystogram. Operation was not performed until several days later. On the assumption that his disease was of such short duration that recovery to a fairly normally functioning gall bladder may have taken place after the lapse of a few more weeks, we admit that we probably made an error in advising operation at this time. It is quite obvious however, that a fold offering so much chance for obstruction, particularly when edematous, would sooner or later be responsible for the development of a serious cholecystitis. As stated, slight thickening and mild inflammatory reaction were already present. The error made in this case would have been much greater if the initial obstruction had been caused by an acute inflammation in the absence of any anomalous obstructive lesion.

Recovery of the gall bladder from a diseased state when no shadow is obtained on cholecystogram, to a state when a normal shadow is revealed a few weeks later, was noted as early as 1927 by Lyon and Swalm (11). Since then it has been observed by numerous radiologists (Jenkinson (14) et al). The explanation is obvious. Any tissue can be temporarily diseased and lose its function and after subsidence of the inflammation return to a relatively normal status. We would naturally not expect the gall bladder to be an exception to this simple axiom. Unfortunately, a gall bladder would probably not stage many recoveries of this type, but after a few recurrent attacks would probably fail to show a shadow on the cholecystogram.

5. *Stone in the cystic duct.* As stated previously the lodgment of a stone in the cystic duct frequently produces complete obstruction, resulting in hydrops or empyema of the gall bladder, but much more frequently produces a partial obstruction or a complete one of short duration. Case 7, a woman 37 years of age, complaining of severe attacks of colicky pain of five months duration is a perfect example of partial obstruction of this type. At operation the gall bladder was not distended and appeared quite normal. The wall was bluish in color and not thickened. The gall bladder contained deeply colored bile and numerous small mulberry cholesterol stones. One was lodged in a cup-like fold of Heister (see Fig. 7) and was so completely surrounded by the fold that it appeared to be encysted. Cholecystogram revealed no shadow. Since the gall bladder appeared so normal, it seems safe to assume that the stone, though small, was encroaching on the lumen sufficiently to prevent the entry of enough bile to allow the development of a shadow on the cholecystogram.

6. *Tension induced by enlarged liver.* Several years ago Alexander and Bond (15) noted that cholecystograms performed on patients with enlarged livers usually revealed no shadow of the gall bladder in spite of the fact that at operation or post mortem examination there might be no evidence of cholecystitis or bile duct disease. The explanation of this would probably lie in two possibilities, first that the tension on the duct produced sufficient compression to prevent filling, or second, that the functions of the gall bladder itself were affected in some unknown manner secondary to the hepatic disease. The former explanation seems much more plausible.

7. *Compression or filling defect due to tumors or*

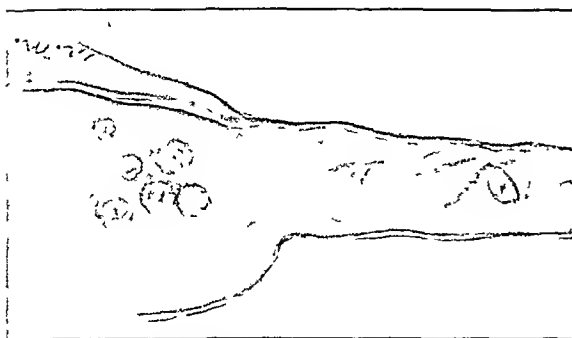


Fig. 7. Case 7. A stone is lodged in a Heister fold, and is encysted so completely that it could not be extracted without cutting the fold. Cholecystogram showed no shadow, even though the fundus of the gall bladder appeared normal. Several small stones were found in the gall bladder. It appears likely that the obstruction produced by the stone encysted in the cystic duct prevented the filling of the gall bladder.

enlarged lymph nodes. Tumors of the cystic duct itself are quite uncommon and are usually carcinomatous in type. Compression by enlarged lymph nodes is likewise uncommon but metastases from various sources may become implanted in the nodes about the cystic duct and produce partial or complete obstruction. Acute inflammation of the "sentinel" or cystic node might rarely obstruct the duct. Since the obstruction produced in the ways mentioned above are usually gradual, symptoms would be insidious. Severe pain of the type produced by stone in the duct or other comparatively sudden mechanisms will not be experienced.

8. *Obstruction due to anomalous hepatic or cystic artery.* Obstructions due to anomalous arteries are likewise uncommon and would likely be gradual in development.

SIGNIFICANCE OF DELAYED EMPTYING OF THE GALL BLADDER FOLLOWING THE FAT MEAL IN CHOLECYSTOGRAPHY

Previous to the present study, we were undecided as to the amount of diagnostic value that could be attributed to delayed emptying of the gall bladder following the fat meal during cholecystography. We are quite convinced now that at least on certain occasions much information can be gained from this delayed response of the gall bladder to the meal. Confirmation by examination of the gall bladder and cystic duct as removed at operation gives support to the supposition that delay in emptying may at least on some occasions be of definite diagnostic value. Normally there will be a sharp diminution in size of the cholecystographic shadow one hour after the fat meal. There may not be much decrease in density because the gall bladder has not had time to accumulate much bile and dilute its contents. Not infrequently the shadow has disappeared entirely.

Cases 1, 2 and 3 show a marked delay in emptying of the gall bladder following the fat meal. Each patient (see protocol of cases) complained of severe pain in the right upper quadrant with radiation posteriorly and other manifestations quite typical of gall bladder disease. Two of them had had a cholecystostomy previously, with relief for a time, but it is doubtful if this factor is of significance in interpretation of the findings. It seems obvious that the few adhesions

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The fact that the gall bladder wall showed so little evidence of inflammation in the three cases described above, and that a definite lesion of obstructive character was found in the cystic duct along with failure of the gall bladder to empty following a fat meal has been interpreted as indicating that emptying was prevented by the lesion in the cystic duct. Although it is obvious that bile was able to enter the gall bladder an explanation of the inability to empty must be found. It is our opinion that the increased viscosity of the bile leaving the gall bladder was one of the most important mechanisms in the inability of the gall bladder to empty. Whether or not the position of the cystic duct in situ before removal at operation had any influence on the production of a valvular mechanism

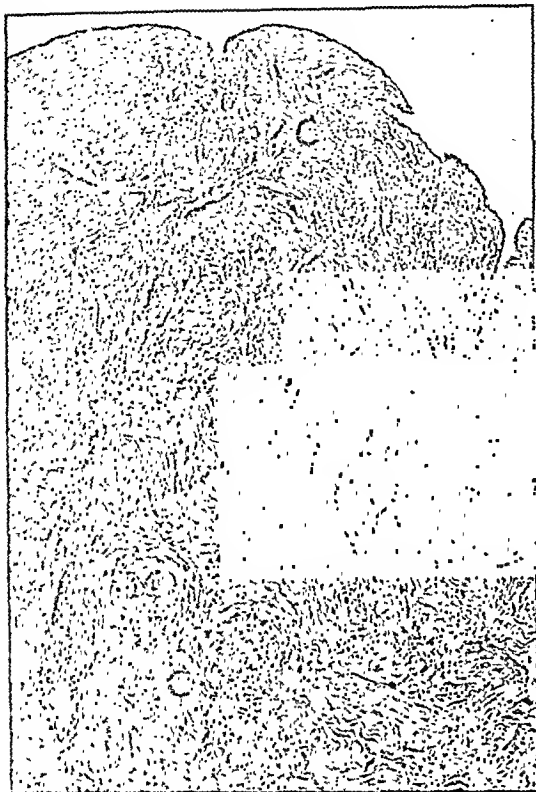


Fig. 1. Microscopical section of the nodule projecting into the lumen as shown in Fig. 5. The lesion consists of connective tissue (C) in which a few muscle bundles (MI) are seen. It appears to be the residue of an ulcerative process, possibly associated with the gall stones. In proof of this assumption is the fact that the scar is densest at the mucosal side near the lumen.

bladder wall was diseased sufficiently to cast doubt as to the ability of the organ to concentrate, thereby making it difficult to tell whether the lack of shadow on the cholecystogram was caused by an obstruction of the cystic duct or by disease of the gall bladder wall.

Structures due to scar formation are undoubtedly common and probably account for the great majority of cases of hydrops or empyema of the gall bladder in which no stones are found.

Valve-like anomalies are probably congenital in origin and are quite frequent. Originally they were apparently large folds of Heister but became cup shaped because of the pressure exerted by viscid bile and concretions or stones from the gall bladder side. The fact that their concavity practically always faces the gall bladder suggests that they have acted as an obstruction to the contents of the gall bladder while being expelled through the duct. Case 5, a man aged 37, with pain of only three months duration, had a large well formed cup shaped valve-like fold at the junction of the cystic duct and neck of the gall bladder where the lumen was still 6 to 8 mm. in diameter. When filled this cup shaped fold, which extended all the way across the duct undoubtedly acted as a serious obstruction. Obviously, when collapsed, bile could enter the gall bladder without difficulty. If edematous it would obviously produce an obstruction in both di-

rections. Cholecystogram revealed no shadow, but it was performed a few days after an acute attack of right upper quadrant pain. Unfortunately, we did not get a later cholecystogram. Operation was not performed until several days later. On the assumption that his disease was of such short duration that recovery to a fairly normally functioning gall bladder may have taken place after the lapse of a few more weeks, we admit that we probably made an error in advising operation at this time. It is quite obvious however, that a fold offering so much chance for obstruction, particularly when edematous, would sooner or later be responsible for the development of a serious cholecystitis. As stated, slight thickening and mild inflammatory reaction were already present. The error made in this case would have been much greater if the initial obstruction had been caused by an acute inflammation in the absence of any anomalous obstructive lesion.

Recovery of the gall bladder from a diseased state when no shadow is obtained on cholecystogram, to a state when a normal shadow is revealed a few weeks later, was noted as early as 1927 by Lyon and Swalm (11). Since then it has been observed by numerous radiologists (Jenkinson (14) et al). The explanation is obvious. Any tissue can be temporarily diseased and lose its function and after subsidence of the inflammation return to a relatively normal status. We would naturally not expect the gall bladder to be an exception to this simple axiom. Unfortunately, a gall bladder would probably not stage many recoveries of this type, but after a few recurrent attacks would probably fail to show a shadow on the cholecystogram.

5. *Stone in the cystic duct.* As stated previously the lodgment of a stone in the cystic duct frequently produces complete obstruction, resulting in hydrops or empyema of the gall bladder, but much more frequently produces a partial obstruction or a complete one of short duration. Case 7, a woman 37 years of age, complaining of severe attacks of colicky pain of five months duration is a perfect example of partial obstruction of this type. At operation the gall bladder was not distended and appeared quite normal. The wall was bluish in color and not thickened. The gall bladder contained deeply colored bile and numerous small mulberry cholesterol stones. One was lodged in a cup-like fold of Heister (see Fig. 7) and was so completely surrounded by the fold that it appeared to be encysted. Cholecystogram revealed no shadow. Since the gall bladder appeared so normal, it seems safe to assume that the stone, though small, was encroaching on the lumen sufficiently to prevent the entry of enough bile to allow the development of a shadow on the cholecystogram.

6. *Tension induced by enlarged liver.* Several years ago Alexander and Bond (15) noted that cholecystograms performed on patients with enlarged livers usually revealed no shadow of the gall bladder in spite of the fact that at operation or post mortem examination there might be no evidence of cholecystitis or bile duct disease. The explanation of this would probably lie in two possibilities, first that the tension on the duct produced sufficient compression to prevent filling, or second, that the functions of the gall bladder itself were affected in some unknown manner secondary to the hepatic disease. The former explanation seems much more plausible.

7. *Compression or filling defect due to tumors or*

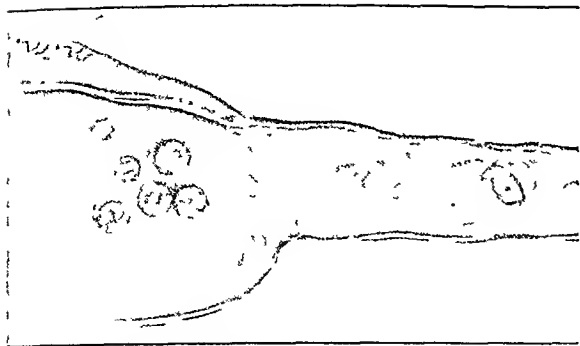


Fig. 7. Case 7. A stone is lodged in a Heister fold, and is encysted so completely that it could not be extracted without cutting the fold. Cholecystogram showed no shadow, even though the fundus of the gall bladder appeared normal. Several small stones were found in the gall bladder. It appears likely that the obstruction produced by the stone encysted in the cystic duct prevented the filling of the gall bladder.

enlarged lymph nodes. Tumors of the cystic duct itself are quite uncommon and are usually carcinomatous in type. Compression by enlarged lymph nodes is likewise uncommon but metastases from various sources may become implanted in the nodes about the cystic duct and produce partial or complete obstruction. Acute inflammation of the "sentinel" or cystic node might rarely obstruct the duct. Since the obstruction produced in the ways mentioned above are usually gradual, symptoms would be insidious. Severe pain of the type produced by stone in the duct or other comparatively sudden mechanisms will not be experienced.

8. *Obstruction due to anomalous hepatic or cystic artery.* Obstructions due to anomalous arteries are likewise uncommon and would likely be gradual in development.

SIGNIFICANCE OF DELAYED EMPTYING OF THE GALL BLADDER FOLLOWING THE FAT MEAL IN CHOLECYSTOGRAPHY

Previous to the present study, we were undecided as to the amount of diagnostic value that could be attributed to delayed emptying of the gall bladder following the fat meal during cholecystography. We are quite convinced now that at least on certain occasions much information can be gained from this delayed response of the gall bladder to the meal. Confirmation by examination of the gall bladder and cystic duct as removed at operation gives support to the supposition that delay in emptying may at least on some occasions be of definite diagnostic value. Normally there will be a sharp diminution in size of the cholecystographic shadow one hour after the fat meal. There may not be much decrease in density because the gall bladder has not had time to accumulate much bile and dilute its contents. Not infrequently the shadow has disappeared entirely.

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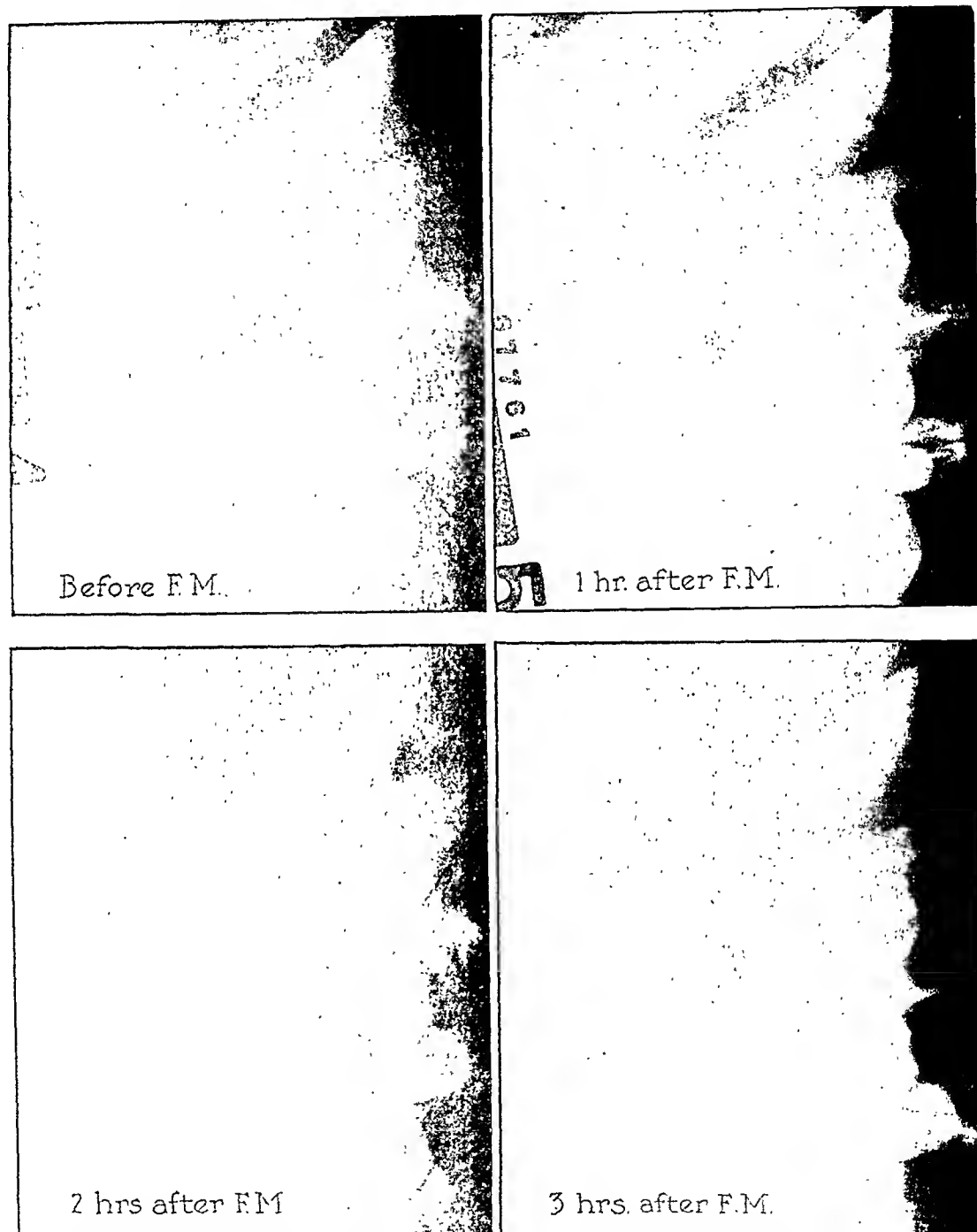


Fig. 8. Response of the cholecystographic shadow to the fat meal in Case 1. Note that there was an initial decrease in size of the shadow but at the end of 3 hours a dense shadow is still seen. The gall bladder wall was only slightly diseased, but the cystic duct was stenosed and buried in dense adhesions. It appears that the dense fibrous tissue and the coincidental stenosis acted as an obstruction perhaps explaining the patient's symptoms and the failure of the gall bladder to contract normally after the fat meal.

cannot be determined. The cystic duct is so small that the occasional presence of a valvular action produced by anatomical lesions and adhesions does not appear hopelessly fantastical. The symptoms of these patients were very similar to those complained of by patients who have stones lodged or encysted in the cystic duct (e.g. Case 7). This fact again brings up the question as to whether the pain is produced by the presence of the stone in the gall bladder or by the gall bladder's futile efforts to empty itself when stimulated to do so. It is naturally difficult to determine this since in a given case of stone in the cystic duct, both mechanisms exist.

All these patients were relieved of their pain. Case 3 gained fifty pounds, however, and is now complaining of pain in the lumbosacral region and in the cardiac region, but none in the right upper quadrant where pain was very severe on entrance.

The three cases showing failure of the gall bladder to empty following the fat meal do not represent all the cases of that type observed during this study, but represent the ones showing obvious obstructive lesions. Others have been observed but no lesions of an obstructive character in the cystic duct were found. In one case the shadow was deformed as if the gall bladder were folded upon itself. At operation a dense band of adhesions was found extending from the liver across the gall bladder and attached to the duodenum. The fundus was therefore fixed, and any muscular activity on the part of the gall bladder would appear to be restricted or eliminated entirely.

SUMMARY

While examining the gall bladders from routine cholecystectomies during the past year or two several instances of partial obstruction of the cystic duct were encountered. A classification of the various types of lesions which are apt to produce partial obstruction has been discussed. Important lesions in this group are adhesions, kinks, an acute inflammatory process, anomalous folds of Heister, stone in the cystic duct and compression by extrinsic factors. Complete obstruction such as illustrated by hydrops and empyema is not discussed because the mechanisms of production and pathology are so clearly understood. It is obviously very difficult to prove that a given lesion of the cystic duct is producing an incomplete obstruction, but an analysis of the cases studied has led us to believe that on many occasions the lesion in the cystic duct represents perhaps the only significant lesion of the gall bladder and that on other occasions it may be the instigating factor of disease in the gall bladder. It is difficult to demonstrate the obstruction experimentally, not only because a criteria of the degree of obstruction based on the rapidity of flow of bile of a given viscosity through the cystic duct would be difficult to establish, but also because of the fact that accurate reading could only be obtained after cholecystectomy. Removal of the gall bladder would of necessity destroy the attachment of the cystic duct thereby altering the factors producing the obstruction, because fixation and adhesions are bound to be important factors in a great majority of the obstructions even though the primary lesion may be a congenital anomaly involving the folds of Heister.

It should be emphasized that in a great majority of instances, an anatomical lesion may be present without exerting any obstructive influence until an acute

inflammatory process is implanted upon it. There is very good evidence that acute inflammation of the cystic duct occurs commonly. The fact that adhesions about the cystic duct are so commonly encountered in gall bladder disease is in itself fairly good proof. The presence of severe clinical manifestations typical of gall bladder disease, with a demonstrable lesion of the duct in the absence of significant pathologic changes in the gall bladder wall, as was the case in most of the patients studied in this series, is also suggestive proof that the lesion in the cystic duct may be an important factor in the production of the manifestations. This is particularly true if cholecystectomy relieves the patient's symptoms.

A consideration of some of the patients in this series suggests very decisively that at least in some instances the failure of the gall bladder to empty (as determined by cholecystographic study) following the fat meal is indicative of serious cholecystic disease. It is conceivable that the failure of emptying might be due to (1) obstructive lesions of the cystic duct; (2) inefficient muscular response on the part of the gall bladder (e.g. atony) or (3) spasm of the sphincter of Oddi. In this study, however, attention was directed only to mechanisms involved in the first group.

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DISCUSSION

DR. B. B. VINCENT LYON (Philadelphia, Pa.): I consider the paper of Drs. Cole and Rossiter a most interesting one and a most timely one. I feel that they have made an important contribution that sheds new light and gives a probable explanation as to why occasional patients who have suffered severe pain, considered to be gall bladder in origin, make clinical satisfactory recoveries after the removal of an innocent-looking gall bladder. Their studies have pointed out that the lesion lies in the cystic duct and not in the gall bladder. I wish Dr. Cole would later on publish a follow-up of these cases now reported, in regard to their complete clinical improvement.

Their studies also suggest the importance of bearing in mind the likelihood of some form of cystic duct obstruction in all patients who showed delayed or deficient emptying

to cholecystographic study. We should also bear in mind that this delay in emptying is equally observable on biliary drainage.

The normal gall bladder, in my experience, will empty nearly completely on single, or sometimes, multiple stimulations with magnesium sulphate or peptone, or a combination of the two, without having recourse to fatty stimulants such as olive oil or oleic acid. When a gall bladder will respond only to the latter, although physiologically this is believed to be the best stimulant, I consider such a gall bladder to be abnormal to a certain degree.

This sounds paradoxical since it does not check with the emptying response to the fat-full meal during cholecystography, except for the fact that in both there is evidence of delayed or inefficient emptying. But the fault may lie in some lesion producing partial obstruction of the cystic duct rather than lack of proper tonicity of the gall bladder wall.

In 1927, Dr. Swalm and I reported our observations regarding the frequency of partial or temporarily complete obstruction of the cystic duct produced by catarrh or edema, and demonstrated how it can be recognized. We are constantly picking up additional cases in our clinic and practice each year. It is gratifying to report that the majority of these patients have become symptomatically well, with return to normal cholecystograms.

Followed up carefully over a number of years, most patients in this group have not yet developed a surgical form of cholecystitis or of cystic duct obstruction, however, a small minority of these cases who have failed to return to normal cholecystographic response have usually proved at operation to be cases of cholesterosis. It is possible that some of the abnormalities that Cole and Rossiter have described may also be associated with catarrhal obstruction or edema, and it would be most important if we could learn how to segregate this necessarily surgical group, and urge that they be operated upon.

I noted that two of their seven cases (28.5 per cent) have had previous cholecystostomies. This brings up a question as to how frequently this operation achieves complete recovery and how frequently it is followed by relapse. Excepting cholecystostomies for empyema or for acute suppurative cholecystitis, where the operative risk of cholecystectomy is high, I have frequently expressed the opinion that cases submitted to surgery should have sufficient pathology found on operating table to warrant surgical removal rather than surgical drainage of the gall bladder. Such successful results as accrue to surgical drainage of a gall bladder without cystic duct obstruction can be achieved with greater safety by non-surgical biliary drainage.

Also it has been noted by many of us that some surgeons, usually the less skillful, have assumed that cholecystostomy is preferable to cholecystectomy on the ground that if anything should "go wrong", a cholecystectomy or an anastomotic operation between gall bladder and stomach or duodenum may still be done. In the latter case, I believe that the surgeon must make very sure indeed that the cystic duct is not obstructed by any of the conditions Drs. Cole

and Rossiter have pointed out. Otherwise such an operation is a useless procedure with regard to the welfare of the patient.

Again, I congratulate the authors on the worthwhileness of this paper.

DR. ALBERT F. R. ANDRESEN (Brooklyn, N. Y.): It has been very interesting and important to have our attention called to these anatomical conditions causing difficulty in gall bladder emptying. However, one factor which may cause interference both with filling and emptying of the gall bladder has not been brought out. If there has not been sufficiently frequent and forceful stimulation to gall bladder evacuation, its wall may become atonic and its contents too concentrated, the latter interfering with filling, and both with emptying. Persons priding themselves on eating only once a day or who because of digestive symptoms have cut down on quantity and frequency of meals, thereby causing insufficient natural stimulation to the emptying of the gall bladder, will therefore usually show either no gall bladder shadow, or a faint shadow, after dye administration, or if a gall bladder shadow is seen it may show little or no decrease in size after the fatty meal. In such cases it is our custom to prescribe a well balanced diet, with sufficient fat for proper gall bladder stimulation and with an adequate vitamin and mineral content, meanwhile attending to the patient's general condition, removal of focal infections and hygienic measures. After four to six weeks we have another gall bladder series, when in many cases the findings may be normal or there may be found definite evidences of disease, such as stones, deformities or a persistent failure to fill, indicating, possibly, the need for operation.

DR. JOHN R. TWISS (New York, N. Y.): I should like very much to express my appreciation of this very instructive paper and also the privilege of hearing Dr. Lyon and Dr. Andresen discuss it, and to add further a few points from a viewpoint of practical experience.

We have followed Dr. Lyon's method of study in gall bladder disease at the New York Post-Graduate Hospital for a number of years and have studied approximately four thousand patients, doing both X-ray examinations and duodenal drainage on all of them. We have found, as Dr. Andresen has, that in many patients there will be no visualization of the gall bladder on initial examination and with biliary tract drainage no concentrated gall bladder bile obtained. In many cases where gall bladder bile is obtained, it will be only after olive oil and not after magnesium sulphate stimulation, as stated by Dr. Lyon.

I should like to emphasize what Dr. Andresen says, that a trial course of medical treatment is in all cases indicated, especially following repeated duodenal drainage. In many cases these patients will later show normal visualization and be entirely relieved of their symptoms. We feel that operation is indicated only if after a period of trial medical treatment, the patient's symptoms persist and there is persistently no visualization of the gall bladder, and no concentrated gall bladder bile obtained on drainage.

The Endocrines in Relation to the Gastro-Intestinal Tract*

By

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I THINK that it is peculiarly fitting that gastroenterologists are interested in endocrinology, since it may be truly said that modern endocrinology, so much dependent as it is upon the isolation of active principles from endocrine glands and tissues, originated in the gastro-intestinal field. I refer, of course, to the epoch-making discovery of duodenal hormone secretin by Bayliss and Starling in 1902 (1). Sir Frederick Gowland Hopkins was present on this memorable occasion, and in a recent writing (2) he recalls the incident as follows: "It was my privilege to be present at University College, London, on the very day (Jan. 16, 1902) when Bayliss and Starling first made the *experimentum crucis* which definitely established the existence and functions of secretin as a chemical entity. I saw with them for the first time a copious secretion flow from the duct of a completely denervated pancreas of a dog as the result of injecting intravenously an extract from the intestinal epithelium. I remember too the day, a little later, when a discussion at Gonville and Caius College, Cambridge, led Starling to select the name Hormone for secretin and substances with analogous functions.

Bayliss and Starling used dilute hydrochloric acid to prepare their extract of the duodenal mucosa, but since they were able to show that intravenous injection of the acid alone had no secretagogue action they concluded that the positive effect of their extract was due to an active principle obtained from the duodenal tissue. They showed also that the introduction of acid into the duodenum produced a copious secretion of pancreatic juice even though the intestinal segment had previously been denervated.

Ivy and co-workers (3) transplanted a loop of intestine and the tail of the pancreas under the skin, thus severing their nerve connections, and found that the introduction of acid into the isolated duodenum produced a secretion from the pancreatic transplant. Since the intravenous injection of acid alone proved ineffective, these experiments gave conclusive proof of the hormonal mechanism of activation of the pancreatic acinar cells. Mellanby and Huggett (4) demonstrated that secretin exists preformed in the mucosa, from which it can be extracted by water, alcohol and other solvents, as well as by dilute acid.

In view of the primitive nature of the gastro-intestinal tract and the glandular appendages derived therefrom, it is to be expected that many hormonal mechanisms of an essentially local character would be developed. For the same reason it could be predicted that the digestive tract would be less under the control of those endocrine glands which embryologically have a different origin than are other organs and tissues of mesoblastic or ectodermal origin. There are definite functional interrelationships between various glands such as the pituitary, the parathyroids and the suprarenals, and the gastro-intestinal tract, but these I

think, are of more recent development than is, for instance, the control of the thyroid, the suprarenal cortex and the gonad by the anterior pituitary.

Since the discovery of secretin by Bayliss and Starling, much experimental evidence has been published showing the existence in and extraction from parts of the alimentary tract of other hormones or hormone-like substances. Thus Edkins in 1906 (5, 6) and Edkins and Tweedy in 1909 (7) found that a hydrochloric acid extract of the pyloric mucosa had a powerful secretory effect upon the gastric glands when injected intravenously. They attributed this effect to the presence of a special hormone "gastrin" which they thought is liberated into the blood stream during digestion.

Later work by Koch, Luckhardt and Keeton (8), in which it was shown that extracts of other tissues have a gastric secretagogue action, deprived the work of Edkins of much of its physiological significance. It was shown by Popielski (9, 10) that histamine is a powerful stimulant of gastric secretion, and the "gastrin" effect was attributed thereafter by many to histamine. Ivy and Farrell (11, 12) and Kim and Ivy (13) were able to demonstrate that there is a secretagogue substance actually present in the blood during digestion. Very recently Komarov (14), working in Babkin's laboratory, has obtained an extract of pyloric mucosa by the use of trichloroacetic acid which is said to be free of histamine, choline and other organic crystalloids, and which is a powerful secretagogue. If this work is subsequently confirmed, it would appear to establish on a definite and firm basis the original "gastrin" theory of Edkins.

Ivy and Oldberg (15) have extracted from the duodenum a substance which causes contractions of the gall bladder. They have been able to remove histamine and other vaso-dilator substances from their extracts and still retain the specific physiological activity. They have named the substance "cholecystokinin".

Another intestinal hormone termed "enterogastrone" has been extracted from intestinal mucosa by Gray, Bradley and Ivy (16). This substance has the property of inhibiting the hunger contractions of the dog's stomach, and the secretory effect of injected histamine.

Ludany and co-workers (17, 18, 19, 20) claim to have extracted from the mucosa of the stomach and small intestine a principle which stimulates the movements of the intestinal villa and the name "villikin" has been suggested for this substance. The introduction of hydrochloric acid into the duodenum is said to increase the production of villikin and at the same time the absorption of glucose is facilitated (21). In isolated loops of jejunum villikin administration likewise increased the rate of glucose absorption (22). The authors suggested that this hormone is present in the intestinal mucosa in the form of a prohormone

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which can be activated by hydrochloric acid since they were able to extract an inactive precursor by other means (23).

In a recent communication, Nasset, Schriffrin and Belasco (24) extending the earlier work of Nasset, Pierce and Murlin (25) and of Nasset (26), appear to have established that an intestinal secretory hormone "enterocrinin," distinct from secretin, can be extracted from both the small and large intestine of dogs and pigs. Enterocrinin acts upon the intestinal glands, causing an increase both in volume and in enzyme content of the succus entericus. Acid in the intestine is not the stimulus for the liberation of enterocrinin as it is for secretin, since hydrochloric acid introduced directly into the duodenum in acute experiments did not excite the glands of isolated segments of jejunum to secrete intestinal juice. It caused a marked increase in the oxygen consumption of isolated dog intestinal mucosa. This work of Nasset and coworkers on the isolation of an intestinal secretagogue fits in well with the demonstration by Florey and Harding (27) that the glands of Brunner are under hormonal control. These authors observed an active secretory process after the ingestion of food in the transplanted duodenum, all nerve connections to which had been severed.

All of the hormonal mechanisms thus far mentioned have been more or less local and circumscribed. It should be mentioned in passing that the haemopoietic substances found in the stomach and liver may be considered as belonging to the hormone group. These substances presumably have a zone of activity outside of the gastro-intestinal tract.

Extracts have been prepared from intestine by various methods, and by different workers, which have the property of producing hypoglycemia (28-38). It is possible that further work along these lines will in the future establish some important connection between the intestinal mucosa and some phases of carbohydrate metabolism, more especially those relating to clinical diabetes.

Recently Hallier (39) has published an extensive study of the basal granulated (also known as the argentaffin) cells of the intestine in the guinea pig and rabbit. He claims that prolonged treatment with thyroid hormone or posterior pituitary extract decreases their number while insulin has no effect upon them. In this connection attention should be called to the fact that the argentaffin granules in the intestine have frequently been regarded as identical with adrenalin, and Feyrter and Unna (40) were able to extract a pressor principle from an argentaffin carcinoid tumour of the appendix. The action of this extract could be reversed by ergotoxin just as that of adrenalin can be reversed.

Petri (41) made the observation that removal of the stomach and the first part of the duodenum causes the appearance of pellagra-like symptoms in young dogs. It is interesting that oral administration of large quantities of the vitamin B₂-complex did not cure this condition, although it makes its course somewhat milder. The author compares these findings with the ineffectiveness of vitamin B₂ treatment in some acute cases of pellagra in man and thinks that the condition is due to an inability of the organism to utilize orally administered vitamin B₂ in the absence of the stomach and duodenum.

It is probably safe to assume that the normal func-

tioning of the gastro-intestinal tract in the intact individual is associated with the continuous action of a number of hormones arising from various endocrine glands. It is difficult to single out very many specific effects of hormones upon the gastro-intestinal tract. The maintenance of normal water and salt content of the tissue must be of prime importance, and here as elsewhere the suprarenal cortex and the parathyroid glands no doubt have much to do with regulation of these factors.

The whole neuromuscular mechanism of the gastro-intestinal tract is responsive to adrenalin and acetylcholine, and glandular activity is modified by these same active principles.

That pituitary hormones are not essential for the functioning of the gastro-intestinal tract is shown by the failure of hypophysectomy to produce any well-defined changes in the digestive functions. Splanchnomegaly has been produced in dogs by the administration of anterior lobe extracts and in the pigeon Riddle and co-workers have shown that prolactin causes a considerable degree of enlargement of the liver. More recently Bates, Riddle, Lahr and Schooley (42), in an extension of this latter study, found that prolactin may also produce a relative over-growth of the intestines both in the normal and hypophysectomized pigeon. Prolactin did not produce splanchnomegaly in the rat, but Best and Campbell (43), using other anterior lobe preparations, obtained marked enlargement of the liver with fatty infiltration in this species.

While referring to the anterior lobe mammary secretagogue prolactin, it is of interest to note that the crop gland of the pigeon, although part of the alimentary tract, may be regarded as the equivalent in this form of the mammary gland of the mammal. Riddle (44) discovered that the crop gland can be stimulated to enlarge and produce crop milk, and has made use of this response in the immature dove or pigeon to assay and standardize prolactin. Later Lyons and Page (45, 46) showed that this test can be made much more sensitive if the extract to be tested is injected intradermally over the crop sac area.

In 1910, Franchini (47) found that pituitary extracts, especially those of the posterior lobe, caused ulcerations in the gastric and intestinal mucosa of the guinea pig and rabbit. More recently, Dodds and his co-workers (48) made similar observations and considered the possibility that this action of posterior lobe extracts may be due to a special "gastrotoxic factor." Hanke (49) produced similar changes using adrenalin or insulin, and these findings have been confirmed by Selye, Stehle and Collip (50) who showed, furthermore, that adrenalectomy or partial hepatectomy sensitizes the rat considerably to this action of adrenalin, pituitrin or insulin. The latter authors, using purified preparations of the oxytocic, melanophore and vasopressor principle showed, furthermore, that in pituitary extracts it is the latter hormone which is responsible for the production of these ulcers. Since it has been proven that not only hormones but various other damaging agents cause similar gastric ulcers (Selye (51)) further experiments would have to be performed before one could regard the findings of Dodds as a significant proof of the existence of a specific interrelationship between the posterior lobe and the gastric mucosa. In this connection, one might also mention that posterior lobe extracts may inhibit the gastric secretion otherwise produced by histamine

(Dodds, et al 52, 53)). In fact an inhibitory action of these extracts on the secretion of the stomach was observed as early as 1916 by Pal (54). Gastric motility is increased following administration of posterior lobe extracts in man (Zanasi (55)).

In conclusion I would call to your attention the peculiar effect of the thyroid hormone upon calcium metabolism. Exhibition of this hormone may cause a great increase in the elimination of calcium salts. The increased excretion of these is almost entirely by bowel. This is in sharp contrast to the effect of the parathyroid hormone which causes a great increase in calcium excretion, but here nearly all of the excretion is by way of the kidney.

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DISCUSSION

DR. ANDREW C. IVY (Chicago, Ill.): Mr. President, Ladies and Gentlemen: This excellent review does not call

for much discussion. There is really nothing to add. However, I should like to have heard Dr. Collip spend a little more time on the hormone called duodenin.

I have followed the literature on that phase of the gastro-intestinal hormones very closely, but have done no work on duodenin. I do not think that the crucial experiment, showing that duodenin actually exists, has yet been performed. I should like to ask Dr. Collip to say a little more about duodenin.

DR. VICTOR C. MYERS (Cleveland, Ohio): I doubt if I am competent to make many comments on Dr. Collip's excellent review. Of course, we are all aware of Dr. Collip's standing in the field of endocrinology, although from conversation I have just had with him, I doubt if in recent years his interest has been particularly in our field of gastro-enterology.

As you know, it was Dr. Collip whom Dr. Macleod called upon to make the first clinical preparations of insulin, and it was Dr. Collip who early made an active extract of the parathyroid gland. His opinions regarding this whole field are authoritative opinions even though in this presentation most of his statements may have been taken from the literature.

DR. WALTER G. KARR (Philadelphia, Pa.): I really haven't anything to add to this excellent presentation and review of Dr. Collip's. Certainly gastro-enterologists should realize the great advances that have been made since the time that we considered the stomach a dumping and mixing bag and the intestine a mere channel for digestion and absorption. The relation of the autonomic nervous system and various hormones to problems of absorption is of especial interest. Dr. Collip didn't mention some work which I have been slightly interested in; the relation of the adrenal gland to absorption from the gastro-intestinal tract, and I wonder what he thinks of the work of Verzar and associates, and how important he considers it to be.

DR. THOMAS R. BROWN (Baltimore, Md.): I should like to ask a question. Dr. Collip's paper brought back the days when I was working with Starling and Bayliss at the University and saw some of the preparations. I should like him to speak a little bit about the increased and diminished activity in certain of these endocrine glands, thyroid, both as to the secretory and absorptive phases.

DR. BORIS P. BABKIN (Montreal, P. Q., Canada): It was a great pleasure to listen to Dr. Collip's presentation and to learn that he is interested in the effect of different hormones on the gastro-intestinal tract. There is no doubt that with his ability and mastery he could add very much to our knowledge about the relations between the endocrine glands and the alimentary canal.

He said very modestly that the effect of the endocrine glands on the gastro-intestinal tract is not very great. That is not quite so, I think. There are indications that in many respects the functions of the gastro-intestinal tract are influenced by the endocrine glands. Consider, for instance, the effect of the parathyroid glands on the gastric secretion. In such case the nervous phase of the gastric secretion is diminished, whereas the chemical phase is increased, which results in a hypersecretion. Therefore it is quite possible that the hypofunction of the parathyroid glands may play a certain part in the hypersecretory state of the stomach. I am convinced that it is a very promising field, and, if Dr. Collip will be interested in the application of his knowledge to the problem of that kind, gastro-enterology will gain greatly.

DR. JAMES B. COLLIP (Montreal, Canada, closing the discussion): Mr. Chairman, I wish to thank the various discussers for their remarks.

As Dr. Ivy may suspect, I deliberately avoided entering upon any detailed discussion on this vexing question about duodenin; however, for those who wish, I have included

ten references in the paper. I am very much puzzled over this whole thing. You all know that in the early days, I think about 1925, Dr. Ivy and his coworkers obtained a definite insulin reaction from some extracts which they prepared from duodenal mucosa. I am not certain whether they got results from gastric mucosa. So it can be said that there is very definite evidence in the literature that insulin or an insulin-like substance may be extracted from intestinal mucosa.

There have been a number of capable people working on this question of extracts of duodenum which supposedly influence carbohydrate metabolism. I am thinking particularly of Dr. LaBarre and his coworkers, and one wonders, when LaBarre has published such clear-cut results, why there has not been confirmation after all these months, and even years. If LaBarre's work is ever confirmed, I would be inclined to be much more convinced that there is such a substance.

I am sorry that I cannot answer Dr. Karr's question about the influence or the possible effect of the suprarenal upon the gastro-intestinal tract. Personally, I do not think that it is fair to consider what happens in an animal in

which the suprarenals are completely removed, or what happens in an animal which one renders practically moribund by giving excess doses of parathyroid hormone. In both of these cases, as has been shown in the case of the dog, renal insufficiency develops, and I myself showed in connection with the parathyroid hormone that one may get profound changes, seen both by gross and microscopic examination, in the mucosa—chiefly in the stomach.

I also deliberately refrained from saying much about the effect of the different endocrines on the gastro-intestinal tract because I do not think that we know very much about it. I am delighted to tell you that Dr. Babkin tells me that he is going to undertake—with his own special methods and with his own special skill—a study of the various hormones upon the gastric, pancreatic and intestinal secretion. I will be very happy indeed to collaborate with him in that study if he so desires.

I feel, as he says, that there is a lot to be found out, but until we have this information, perhaps the less said the better. I know practically nothing from personal experience about the effect of thyroid upon gastric secretion.

Treatment of the Hemorrhagic Tendency in Jaundice; with Special Reference to Vitamin K*

By

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and

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THE hemorrhagic diathesis associated with obstructive jaundice has long been a serious cause of mortality and a great handicap to successful surgical treatment. There have been no adequate methods which would foretell the tendency to bleed in such cases and attempts at treatment have been far from satisfactory. Theories in regard to the coagulation defect have been numerous but most of them have been insufficiently supported by objective evidence. It has been shown repeatedly that the hemorrhagic state could not be attributed to a deficiency in calcium, fibrinogen, blood platelets or thromboplastin, and it seems equally certain that the presence of any regurgitated elements of bile in the blood stream was not the causative factor. The conception that hemorrhage might be due to a deficiency of some substance normally absorbed from the intestine and necessary for the coagulation of blood is of recent origin and begins with pioneer work of Dam, which will be considered in a substance necessary for coagulation was lacking, dates concerned, the first evidence which showed that any substance necessary for coagulation was lacking dates from the studies of Quick and his associates, who presented evidence which indicates that in jaundice there is a diminished quantity of prothrombin in the circulating blood and that the deficiency in this substance is responsible for the disturbance of the process of coagulation.

Prothrombin is a component of the plasma pro-

teins known physiologically by its capacity to form thrombin; aside from this fact and its constant association with plasma globulin, little is known of its chemical or physical properties. Perhaps it is best, as suggested by Patek and Taylor (1937), to regard prothrombin as a physiologic complex rather than as a single chemical substance. Although methods for measuring the prothrombin content of plasma have been little used, within the past few years several conditions have been reported in which there apparently is a diminution in the concentration of prothrombin in the plasma. Such a deficiency occurs in chicks fed on diets lacking in certain fat-soluble substances, in experimental animals with external or renal biliary fistulas, in dogs whose livers have been injured by chloroform and in cattle fed on toxic sweet clover hay. All of these conditions are associated with a well marked hemorrhagic tendency. It is interesting to note that in each of these examples of prothrombin deficiency there is either an exclusion of bile from the bowel, injury of the liver by toxic substances, or a state of nutritional deficiency. There is now good evidence to indicate that the factors common to these forms of the hemorrhagic diathesis have been found.

Between 1929 and 1935, several investigators reported a bleeding tendency among chicks reared on artificial diets but it was not until 1935 that Henrik Dam (8) reported that the deficiency factor responsible for the hemorrhage in these animals was a fat-soluble substance which he designated as "vitamin K" (coagulations vitamin). The bleeding tendency in these chicks was found to be associated with a de-

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crease in the concentration of prothrombin in the plasma and on administration of the nonsaponifiable portion of the fat of the hog liver, alfalfa or other substances that contain the hypothetical vitamin, the bleeding ceased and the concentration of prothrombin rose to normal limits. Time does not permit a retelling of the interesting history of the development of knowledge of Vitamin K; for this and other details, the bibliography of previous articles should be consulted (4, 6, 14, 16, 21). It suffices to say here that Vitamin K apparently is widely distributed in nature; the materials which are known to contain the vitamin, as well as those which have been found to have no protective effect, are mentioned in Table I. Although little is known of its exact chemical and physical properties, it has been prepared in rather concentrated form and has been recently crystallized by Almquist (1937) (2, 3).

The probable relation of a deficiency of vitamin K to deficiency of prothrombin in the plasma of dogs or human beings with biliary fistula or in cases of obstructive jaundice is reasonably clear, since bile acids are required for the normal absorption of fat soluble substances from the bowel and since in the conditions mentioned bile is usually completely excluded. Two factors, the presence of bile in the bowel and a hypothetical fat-soluble vitamin, are therefore known to be of importance in maintaining a normal concentration of prothrombin.

A third and equally important factor remains to be considered, namely, the rôle of the liver in prothrom-

bin deficiency. As will be pointed out, there is both experimental and clinical evidence to show that the liver is intimately concerned in the fabrication, storage or activation of prothrombin, but by just what mechanism this is accomplished is not yet known. Fatal bleeding associated with a low concentration of prothrombin is not uncommon in chronic atrophy (cirrhosis) of the liver, even if the affected person is not deeply jaundiced, and in spite of the presence of bile in the intestine. Chloroform intoxication in animals produced, as Smith and his coworkers have shown, a marked deficiency of prothrombin and a resulting hemorrhagic diathesis. Necrosis of the liver was also demonstrated by Roderick in animals that were dying of the toxic hemorrhagic disease caused by sweet clover hay. Finally, there is some clinical evidence which indicates that in the presence of severe hepatic injury, prothrombin is formed poorly even if Vitamin K and bile salts are administered.

METHODS FOR DETERMINING THE CONCENTRATION OF PROTHROMBIN

Since a large part of the consideration to follow is based upon the results of determinations of the concentration of prothrombin, it is necessary to describe the methods briefly and consider their theoretical basis and adaptability to general use. Such methods are hampered in their application chiefly because of the lack of adequate chemical and physical data on the prothrombin complex itself. Quick and his associates have devised an indirect method which depends on the clotting time of recalcified plasma to which thrombo-

TABLE I
Results of bio-assay of materials for protective substance*

Those containing Vitamin K	Those not containing Vitamin K
Pig liver fat (nonsterol fraction)	Cod liver oil
Dog liver	Wheat germ oil
Beef liver	Carotene
Alfalfa	Carrot roots
Kale	Lemon juice
Dried carrot tops	Chlorophyll
Tomatoes	Beef liver extract (H ₂ O)
Hemp seed	Egg albumen
Soy bean oil	Beef serum and plasma globulin
Egg yolk	Bile from human fistula (pH—8.00)
Fish meal	
Bice bran	
Casein	
Prothrombin of the chick	
Chick feces	
Dried normal human feces	
Dried acholic human feces	
Oat shoots	
Escherichia coli	
Bacillus aerogenes capsulatus	
Bacillus subtilis	

*Materials mentioned in this table represent, in part, the unpublished determinations done by Dr. Bollman and Mrs. Peirce Dunn and the remainder has been collected from previous reports by Dam and Almquist and their associates.

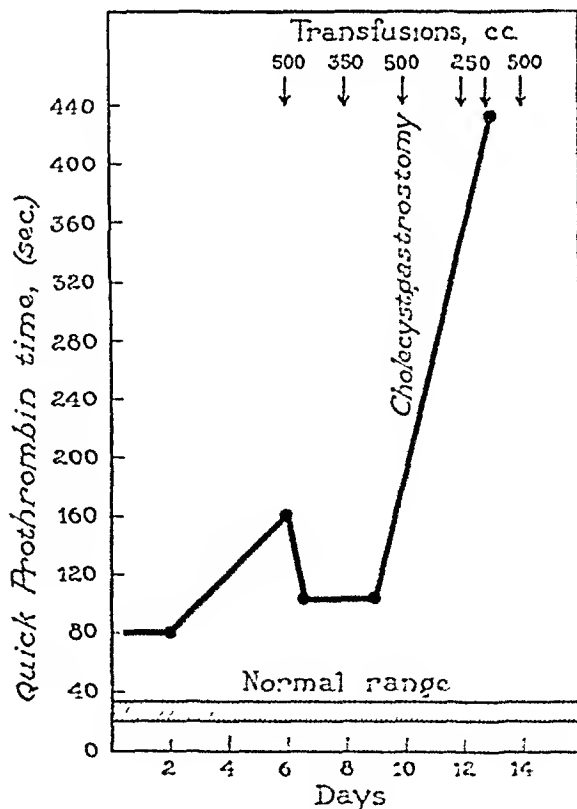


Fig. 1. Prothrombin time in a case of obstructive jaundice with fatal hemorrhage.

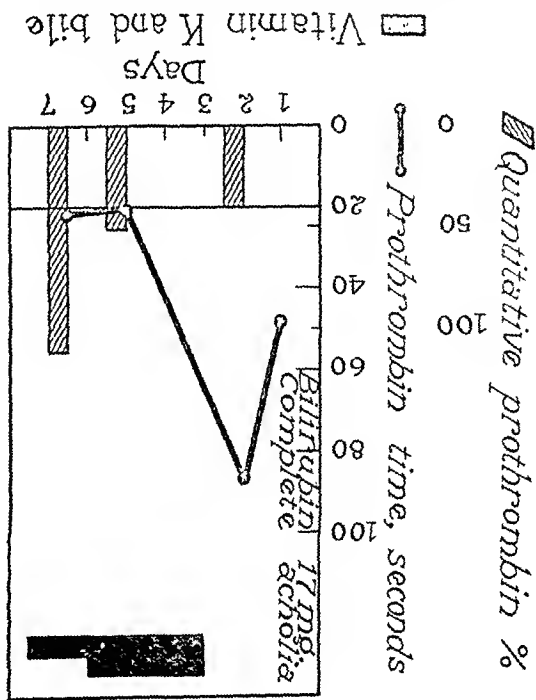


Fig. 2. The effect of Vitamin K and bile on prothrombin clotting time and the concentration of prothrombin in the plasma in a case of obstructive jaundice.

plastin has been added. Since many investigators (18) have shown that fibrinogen is not lacking in jaundiced patients, Quick's method leaves prothrombin as the only variable. The test is simple and gives clinically consistent results which closely parallel those obtained with Nygaard's coagulation index. We have not observed an abnormal tendency to bleed in any jaundiced patient with a normal prothrombin time (twenty seconds); whereas free bleeding may ensue with prothrombin times of from forty-five to one hundred seconds, or higher. In cases in which the prothrombin time is prolonged, surgical or other trauma may initiate bleeding, or it may occur spontaneously. Unfortunately, Quick's method may give normal values even when the concentration of prothrombin is reduced to a dangerously low level. For this reason Quick has suggested that the performance of the test upon serial dilutions of the plasma in question will give an approximate idea of the quantitative reduction of prothrombin and he has constructed a graph of prothrombin time in diluted plasma which can be used for calculation. For practical use the suggestion of Alagath that the determination of the prothrombin time be repeated with plasma diluted with equal parts of physiologic saline solution when the clotting time of the undiluted plasma is less than forty seconds is a valuable one. If there is no marked increase in prothrombin time in the diluted material one may safely assume that the quantitative reduction in prothrombin is not great.

Quick's method may of course be criticized on the noted that the addition of various substances to normal plasma may cause prolongation of coagulation time when this method is used and, therefore, argue that

TABLE II

Comparison of quantitative determinations of prothrombin and prothrombin clotting times in cases of jaundice (in the presence of neoplastic obstruction with complete exclusion of bile from the intestine the greatest deviations from normal are noted)

Prothrombin, percentage of normal concentration in plasma	Prothrombin time (sec.)
105	20
64*	28*
76	20
82*	22*
49*	32*
49	31
35	68
40	86

*Average of two determinations on successive days.

the observed changes do not necessarily indicate a deficiency of prothrombin. So far as the jaundiced patient is concerned, however, the results of the method appear to be satisfactory correlated with the tendency to bleed, a matter which is the principal concern of the clinician. The prothrombin time in a case of obstructive jaundice with hemorrhage rises steadily, as is illustrated in Fig. 1. In spite of repeated transfusions of blood, the prothrombin time in this instance continued to rise and remained elevated until death, which was due to massive intestinal and intraperitoneal hemorrhage.

Dam and Glavind recently have described a method of determining blood coagulation in reference to prothrombin; they have not as yet published a full account of the physiologic basis for this procedure but if their contentions that this method measures the concentration of prothrombin are correct their test gives values which parallel those obtained with Quick's method.

Warner, Brinkhaus and Smith (22) have outlined an elaborate quantitative method for determining the concentration of prothrombin and have employed it extensively in their clinical and experimental studies. With this method the concentration of prothrombin is determined by measuring the second phase of the normal coagulation process, the thrombin formed by prothrombin then being titrated by a method of serial dilution. By using this procedure Smith and his associates have demonstrated that bleeding occurs when the concentration of prothrombin reaches a level of approximately 20 to 30 per cent of the normal; as long as the level remains above this point, no marked prolongation of coagulation time occurs. This establishment of a "critical level" explains why patients with jaundice suddenly and unpredictably begin to bleed before or following operation, since even a small depletion of prothrombin in a patient whose total supply is low might presumably bring the level below the point required for formation of a clot. The quantitative method, unfortunately, is better adapted to a

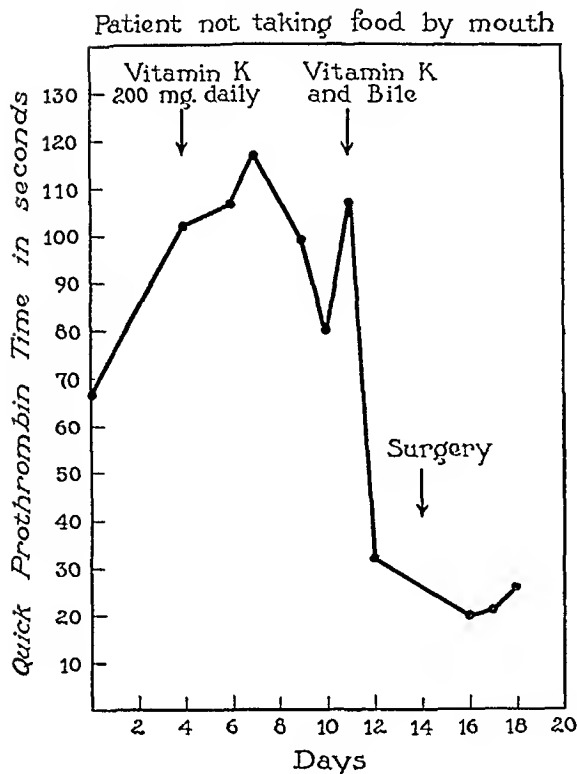


Fig. 3. The effect of Vitamin K alone and Vitamin K with bile on the prothrombin time of a patient with obstructive jaundice.

research laboratory than to general clinical use and is subject to the difficulties inherent in a method employing tissue extracts and serial dilutions. Our experience with it has been limited but in general it confirms Smith's (22) contentions as to the value of the method. The relations existing between the prothrombin time as measured by Quick's method and the quantitative values for prothrombin are reciprocal, at least as the "critical level" is approached, the prothrombin time rising as the value for the concentration of prothrombin falls. A comparison of these figures in a few selected cases is given in Table II.

EFFECTS OF ADMINISTRATION OF VITAMIN K

We have administered to more than thirty patients, most of whom had obstructive jaundice, concentrates containing Vitamin K prepared from putrefied fish meal, together with bile salts or human bile obtained from a biliary fistula. This vitamin preparation was tested on K-avitaminous chicks and found to be protective in doses of 10 to 80 mg. per kilogram of diet.* It is the usual practice to give orally a daily dose of 200 to 1,000 mg. of the material containing Vitamin K, together with bile salts in doses of 1,000 to 4,000 mg. This is probably neither the minimal effective dose nor the optimal one. In some cases human bile that was obtained from biliary fistulas has been given instead of bile salts; it was mixed with cold pineapple juice and given by mouth in doses of 75 to 150 cc. before each meal. In certain cases in which the

patients were very ill and in which a more rapid effect was essential, bile and Vitamin K have been mixed and given through a tube, directly into the stomach or duodenum. A typical response of both prothrombin time and the concentration of prothrombin to Vitamin K and bile when administered together is illustrated in Fig. 2. This effect has been obtained repeatedly, the prothrombin time decreasing to within normal limits within a period of twenty-four to seventy-two hours and the prothrombin itself showing a quantitative increase. Active bleeding has at the same time been controlled in several instances. Warner and his collaborators (23) have independently obtained similar results in clinical practice with a petroleum ether extract of alfalfa meal, as determined by quantitative studies on prothrombin and by clinical observation.

It was obviously desirable to study separately the effects of Vitamin K and bile on prothrombin time in order to determine their relative protective values. In rats with external biliary fistulas Greaves and Schmidt have been able to increase the concentration of prothrombin in whole blood by administering massive doses of Vitamin K. However, as illustrated graphically in Fig. 3, one patient was given Vitamin K in large dosage for one week without any significant alteration in the prothrombin time and not until bile was administered with the Vitamin K was there a reduction of the coagulation time to within normal limits.

The effect of bile on prothrombin time remains to be considered. Judd and Wangenstein have each administered bile obtained from biliary fistulas to certain jaundiced patients with the hemorrhagic tendency and have noted that bleeding was markedly decreased or stopped. Hawkins and Brinkhous have obtained similar effects by the oral administration of bile to dogs with external fistulas who were bleeding actively. We have observed one patient with obstructive jaundice that was due to carcinoma of the pancreas who was able to take an adequate diet but who had complete biliary obstruction as shown by examination of the stools and duodenal contents. Following one week of the daily administration of fresh, alkaline bile which was obtained from biliary fistulas, there was a gradual fall in the prothrombin time to a normal level. The patient was then subjected to cholecystgastrostomy and the prothrombin time remained normal throughout the postoperative period (Fig. 4). These observations ap-

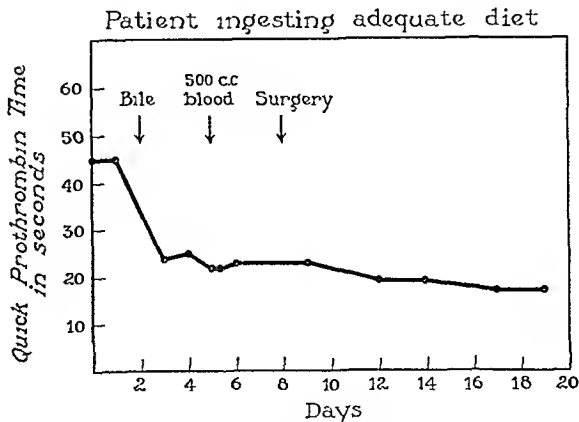


Fig. 4. The effect of bile alone on the prothrombin time in a case of obstructive jaundice.

*We are indebted to Mrs. Clementine Peirce Dann of the Abbott Laboratories, Chicago, and Dr. J. L. Bollman for bio-assay of this material and for their assistance in determining the protective effect of bile and other substances mentioned in the text.

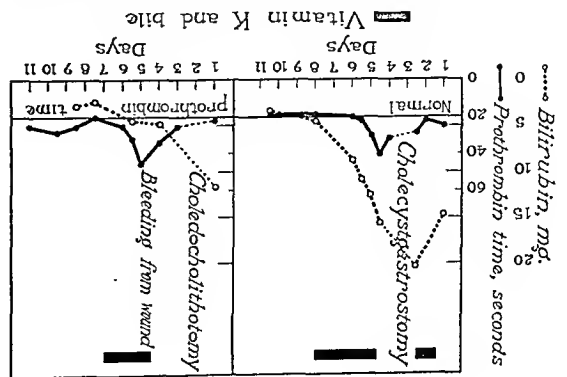


Fig. 5. Postoperative rises in prothrombin time (two cases). These occur even when bile is entering the intestine and when the concentration of serum bilirubin is decreasing.

near to indicate either that bile serves chiefly as a carrier for the fat-soluble vitamin across the membrane of the intestine or that it has in itself some protective effect. It is, of course, known that human stools and those of chicks with K avitaminosis contain the vitamin, which presumably is formed by putrefactive organisms in the intestine. This would explain the source of the vitamin in a case such as that which has just been described. Biologic assays on chicks have shown that human bile obtained from biliary fistulas is weakly protective, presumably because of its high bacterial content and putrefactive processes. In one collection of human bile which was assayed and found to be protective, large numbers of *Bacillus aerogenes* were found growing in nearly pure culture; these organisms have since been shown to contain the protective substance. When a similar lot of bile was collected in acid and immediately autoclaved, it was found to have no protective activity. The evidence, therefore, indicates that bile acts as a medium for transport of the vitamin and has, per se, little antihemorrhagic activity. We have not administered bile alone to a patient who was not ingesting food, nor is there any entirely satisfactory experimental evidence on this point.

CARE OF JAUNDICED PATIENTS BEFORE AND AFTER OPERATION

The method of preoperative preparation of jaundiced patients has been indicated in an earlier paragraph. The administration of bile, bile salts, and Vitamin K has been continued in each instance until either the prothrombin time or the concentration of prothrombin has reached normal limits; the time required was usually short unless marked hepatic injury was present. An adequate diet and the administration of d-glucose intravenously are, of course, still essential in preoperative care. Although one's surgical colleagues may not be inclined to agree, there appears to be little reason to employ preoperative transfusions unless the patient is anemic, since the effects of added blood on either the prothrombin time or on active bleeding are very transient. The greatest danger of hemorrhage following surgical operation for the relief of obstructive jaundice usually occurs between the third and ninth day after operation. This usually is evidenced by a rise in the

prothrombin time, which seems to occur with considerable regularity following operation (Fig. 5). The effect of operation is often sufficient to decrease the concentration of prothrombin in the plasma below the critical level with a corresponding rise in prothrombin time. Whether this is a result of injury of the liver resulting from anesthesia or is due to the loss of blood at operation is not known. Postoperative bleeding may begin as a slight oozing from the wound or, gums, or as hematemesis or melena; it also may become generalized and severe with very little warning. Under such circumstances transfusions of blood are indicated; their effect is to supply a small quantity of prothrombin for emergency use; this exerts its effect for only about six or twelve hours, if at all. During this interval, the administration of Vitamin K and bile may be resumed, preferably by means of the intragastric or duodenal tube. Often, the drop in prothrombin time and the cessation of bleeding which follow are so rapid as to suggest the activity of an enzymic mechanism (Fig. 6). In addition to these two forms of treatment, the importance of beginning an adequate food intake as soon as possible is obvious since the reestablishment of normal biliary flow into the intestine and the restoration of a normal state of nutrition are the ultimate considerations required for cure of the hemorrhagic state. The administration of the vitamin and bile salts should be continued until the concentration of serum bilirubin is within reasonable limits and until the stools contain bile and the prothrombin time is normal.

One great desideratum for postoperative care is the preparation of Vitamin K in a form suitable for intramuscular or intravenous injection. This would avoid the difficulties and dangers of oral administration and undoubtedly would accelerate the restoration of lost prothrombin. The material which we have used is

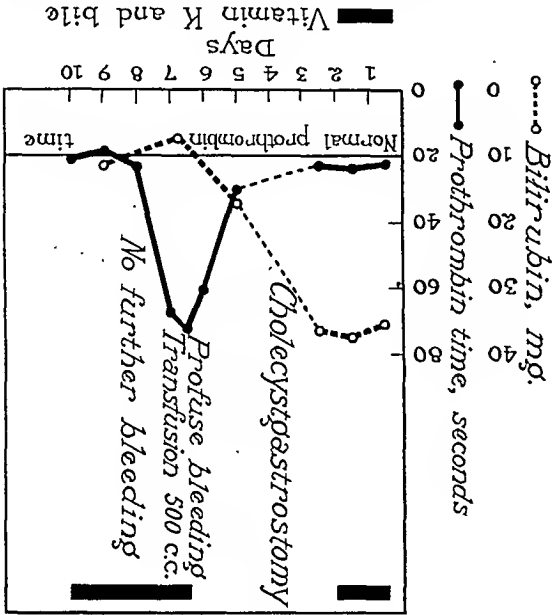


Fig. 6. The effect of Vitamin K and bile on the prothrombin time following cholecystectomy for carcinoma of the pancreas. In this case bleeding stopped following the institution of this treatment.

prepared from putrefied fish meal and is unsuitable for injection, but Dam and Glavind recently have prepared an extract of spinach which can be injected and which has a demonstrable effect on the concentration of prothrombin. When this becomes available one great handicap in the treatment of active bleeding should be easily overcome.

SUMMARY AND CONCLUSIONS

Evidence has been presented to show that oral administration of a fat soluble vitamin and bile salts will increase the concentration of prothrombin and thereby reduce the clotting time of the blood, as measured by both direct and indirect methods. It appears that the vitamin alone will not accomplish this result if bile is excluded from the intestine, while bile or bile salts have some definite effect, presumably because these substances facilitate absorption of the vitamin which is already present in the intestinal tract. The question naturally arises as to why bile alone cannot be used in the preoperative and post-operative treatment. The first reason is, of course, that the prothrombin time may continue to rise postoperatively, even when bile is flowing freely into the intestine. As Warner, Brinkhous and Smith (23) have shown, the administration of Vitamin K greatly accelerates the restoration of prothrombin in such cases. The second is the inadequate food intake which is common to most jaundiced patients and which may of itself lead to depletion of the amount of Vitamin K in the digestive tract. The third factor has to do with the ability of the liver itself to convert the protective material into prothrombin. There is considerable clinical evidence to show that in the presence of injury of the liver larger amounts of Vitamin K are required to achieve the desired effect. Presumably, the chemical laws governing mass action are operative in this connection. A good deal of future experience will be needed before a definite statement as to the indications for and the limitations of this treatment can be established, but for the present it may be said that it offers considerable hope for the ultimate control of the hemorrhagic diathesis in jaundiced persons.

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DISCUSSION

DR. I. S. RAVDIN (Philadelphia, Pa.): The paper by Dr. Snell and his associates is an extremely timely one.

For nearly eighteen years surgeons have been filling their patients full of various calcium salts in an attempt to control the hemorrhagic tendency of the jaundiced patient. In 1929, when we stated from our clinic that calcium salts were useless in the jaundiced patients, we were doubted. The recent investigations of Dam, Greaves and Schmidt, Quick, and those of Dr. Snell's associates at the Mayo Clinic, add an interesting chapter to the problem.

We have obtained a crude source of Vitamin K from the American Butter Company in Kansas City, Missouri, and we have used that for a period of several months. From 1922 to 1929 the incidence of hemorrhage of all degrees in jaundiced patients operated upon in our hospital was 22 per cent; from 1929 to 1933, the incidence of hemorrhage of all degrees was 20 per cent, and from 1933 to 1937, the incidence of hemorrhage was 21 per cent. The mortality in the meantime reduced from 22 per cent to 5 per cent.

It merely meant that we were taking better care of our patients prior to operation and better care of them after operation, which reduced the mortality from operations on jaundiced patients, but, nevertheless although the extent of the bleeding was probably less, the incidence of hemorrhage was as high in 1936 as in 1922. I am happy to say that since our experience has been exactly similar to that Dr. Snell has reported, we have not had a fatal hemorrhage since we began the use of Vitamin K.

It is easy to explain why those patients operated on for duct obstruction, in which bile is flowing into the intestine, either in the method Dr. Snell described or in the method which we reported last year the vitamin may prove inadequate. Such bile contains no bile salt as was shown by Green, Fredrickson, and Walters some years ago, and confirmed by my associates. Under such conditions the amount of Vitamin K absorbed from the intestine may not be adequate to bring the prothrombin time to normal even though bile should be flowing to the intestine.

We have been using hogs' bile, but it seems to me it makes little difference which one uses. Dr. J. E. Rhoads of my service has been using lyophilized hog and human bile and desoxycholic acid.

The use of Vitamin K plus bile, as described by Dr. Snell in this paper, adds a most important chapter in the pre-operative preparation and the post-operative care of the jaundiced patient. Whether one believes it is entirely associated with prothrombin levels or not, the fact remains that prior to the introduction of Quick's method we had no means of telling which patients would or would not bleed. We now have a method of studying and preparing patients before operation and even though the theoretical basis may prove in part to be wrong, the practical application of it is of great value.

DR. ANDREW C. IVY (Chicago, Ill.): Mr. President, and Ladies and Gentlemen: This, obviously, is a very important piece of work, and I have no suggestions or criticisms to offer. I should like to call your attention to certain

D. Bile salts are essential for the absorption of Vitamin D from the intestine. They are also essential for the absorption of Vitamin A. Bile salts also appear to be necessary for the absorption of Vitamin K.

Several years ago Dr. McNealey of Cook County Hospital, Chicago, came to me with the problem of the bleeding tendency in jaundice, and I told him that there might be some connection with the discovery that had just been made showing that bile salts are essential for the absorption of D. I suggested that they give 10,000 units for D three times a day to their patients. I suggested that they use the Duke bleeding time and study the ordinary prothrombin time as it was then performed, but they found no correlation between the clinical bleeding tendency and those determinations. Knowing from the literature that in the hepatic insufficiency of long standing jaundice there may not only be a disturbance of the coagulability of the blood but also of the capillaries, I suggested they place a sphygmomanometer cuff on the arm and raise the pressure to 40 degrees of mercury, causing venostasis, which would tend to put additional stress upon the hemostatic mechanism. When that was done, they found a number of these patients would bleed abnormally long, over a period of four, five, up to ten or fifteen minutes. It was found by controlled operations, that such a patient when operated would bleed post-operatively or manifest serious post-operative disturbances.

When viosterol was given these patients before the operation, along with bile salts, the bleeding time would come back to normal; if the patient's bleeding time did not come back to normal as a result of the administration of the Vitamin D, the patient if operated would die or have a very stormy post-operative convalescence; in other words, the failure to respond to D—and I suspect the same observation will be made in regard to Vitamin K—is of prognostic value and will determine not only the surgical risk but also serve to determine the prognosis in a medical case of hepatic insufficiency.

I should like to ask Dr. Snell if he has observed any surgical or medical patients who have not responded well to Vitamin K; if so, there is another analogy between the action of K and D on the hemorrhagic tendency in jaundice.

There is one other point, one does not have a jaundiced patient to observe a prolonged bleeding time. We have been studying our medical students and each winter we pick out from four to six medical students in our classes who have a prolonged venostasis bleeding time, and they respond to Vitamin D. This past winter we had two women who, when punctured according to our technique not only bled abnormally long but also hemorrhaged into the subcutaneous tissues. The administration of D took care of that disturbance.

DR. RAVDIN: I am interested in what Dr. Ivy has to say. Following the publication of the papers from Dr.

DR. ALBERT M. SNELL (closing the discussion): I am grateful to Dr. Ravdin and Dr. Ivy for their comments and remarks.

I do not want to imply that the only thing we do to prepare a jaundiced patient for operation is to give Vitamin K and bile salts. We insist on the usual pre-operative treatment with glucose and an adequate, high carbohydrate diet, factors which are as essential as they ever were. Cereophyl (formerly called vitola) has been tried in a limited way and has been found to be protective when given to avitaminous chicks in an amount of 100 mg. per kilogram of diet. This assay applies to only one batch but Vitamin K. We are hoping to make concentrates of Vitamin K by extraction of cerophyl with petroleum ether but, until that is done, it is feasible to give the dry powder by mouth.

I am thankful to Dr. Ravdin for mentioning the low concentration of bile salts in the usual specimen of bile obtained from fistulas after operation. No doubt the post-operative inhibition of formation of bile salts has something to do with the post-operative rise in prothrombin clotting time. I presume that the absorption of Vitamin K, in respect to concentration of bile salts in the intestine, follows the laws of mass action. If there is a small amount of bile salts and considerable Vitamin K, a limited rise is obtained; if there is a good deal of both a larger rise results, which I think is an adequate reason for giving large doses of both the vitamin and bile or bile salts, post-operatively.

Failure to respond to treatment with Vitamin K has not been noted if patients have had adequate amounts of bile in the intestine, but we have seen two patients with atrophy of the liver who required large doses and who did not give a too satisfactory response. One man died in hepatic coma, with some bleeding which was hardly sufficient to be a contributing cause of death. I presume the hepatic factor is very important in the utilization of vitamin K to form prothrombin.

Our experience with the Ivy bleeding time has been somewhat limited but by means of it we have not been able to identify all of our bleeders in advance. I think the test deserves a much greater trial than we have given it to date.

Ivy's department, we began the use of what is known as the Ivy bleeding time. As Dr. Ivy has stated we often found prolonged bleeding times in such patients, but we obtained no information as to which patients might bleed and which might not bleed after operation. That is, we did not find it an accurate method of telling us which patients would bleed; patients with perfectly normal bleeding time with the cuff applied showing 40 millimeters of mercury, at times bled seriously after operation.

For a period of several years our patients were fed Vitamin A and D in adequate and abundant amounts, and the incidence of bleeding, in all patients remained approximately the same. Since the introduction of Vitamin K, and bile feedings the incidence has declined sharply.

The Value of a Combined Study of the Newer Laboratory Test in the Differential Diagnosis of Toxic and Obstructive Jaundice Including Blood Phosphatase, Cholesterol Partition, Galactose Tolerance and Glucose Tolerance*

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ALTHOUGH in many instances the differential diagnosis between obstructive and toxic jaundice may be made from the clinical picture alone, it is true that frequently the clinician is forced to seek help in the laboratory. Laboratory procedures subject to difficulties imposed by the peculiar physiology and tremendous reserve of the liver often lose value through attempts to give them too broad a scope. Realizing that any test purporting to help differentiate between toxic and obstructive jaundice must involve some function of the liver and must, therefore, be subject to the above limitations, we decided to combine the various tests that have been proven of some value in jaundice; to do all the tests dependent upon blood examination on the same sample of blood; and to repeat these tests at frequent intervals during the course of the jaundice, extending them whenever possible into the recovery period. By this procedure we hoped to discover the limitations of individual tests; to determine whether individual limitations were dependent upon different factors in the course of the jaundice; and to counteract the limitations imposed by any one test through the combinations of several tests. We hoped, too, to establish more certain criteria upon which to make a differential diagnosis between toxic and obstructive jaundice.

Unfortunately, the laboratory is not the magic slot machine it is sometimes asked to be. This is especially true when utilizing it in the study of jaundice. The variable degree and duration of superimposed obstruction in the finer bile canaliculi in toxic jaundice, coupled with a possible superimposed infection or hepatic cell damage from prolonged obstruction in obstructive jaundice make for a mixed and very often a changing picture.

We have used the quantitative van den Bergh to follow the intensity of jaundice and have compared and contrasted our results with blood serum phosphatase by the Kay Roberts method (1); the total cholesterol and cholesterol esters by the method of Bloor and Knudson (2); the galactose tolerance (3); and the glucose tolerance by the method of Jacobi (4).

GALACTOSE TOLERANCE

Bauer (5) first used the galactose tolerance test to help in the differentiation of obstructive and toxic jaundice. Widely used on the continent, it was not

until 1931 (6, 7) that interest in this test was stimulated in this country where numerous investigators have since confirmed its value.

In the human subject the utilization of galactose makes it ideally suited for testing hepatic carbohydrate function. Its use in obstructive and toxic jaundice, especially in the painless jaundice group of middle and later life, has been stressed (8). More recently because of the conversion of galactose to glucose and its special behavior both as to kidney threshold and utilization, we (3) have recommended that an output over three grams in the five hour test period be checked by fermentation with properly prepared yeast. The technique for the test, as well as the fermentation technique, has been described previously. Reports regarding its value in the differential diagnosis of jaundice have come from many clinics: Rosenberg (9), Schiff and Senior (10), Owen (11), Johnson (12), Tumen and Piersol (13) and Paulson (14) have all found the test of great value.

We have repeatedly stressed the fact that the physiology of the liver, with its tremendous reserve and excellent regenerative power, must put certain limitations upon any liver function test and especially upon one concerned with so vital a function as carbohydrate metabolism.

In obstructive jaundice not complicated by infection, the five-hour output after 40 grams of galactose is below 3 grams, while in diffuse acute parenchymatous liver disease, the output is usually above 3 grams. But in obstructive jaundice with superimposed infection and associated parenchymatous damage, the output of galactose can exceed 3 grams. In the same way, a toxic hepatitis may be mild enough not to alter the carbohydrate function of the liver to cause an excretion of over 3 grams. During the ascent of a severe grade of toxic hepatitis, or in the recovery period, the galactose tolerance may again be normal. A repetition of the test and an interpretation in the light of the clinical and blood bilirubin findings will usually indicate the true state of affairs. No laboratory test will yield 100% results and the galactose tolerance test will occasionally yield a wrong reading for which no suitable explanation can be found; but usually apparently wrong readings if interpreted blindly, will call for an indictment of the observer more often than of the test.

Our present studies indicate all the cases in point

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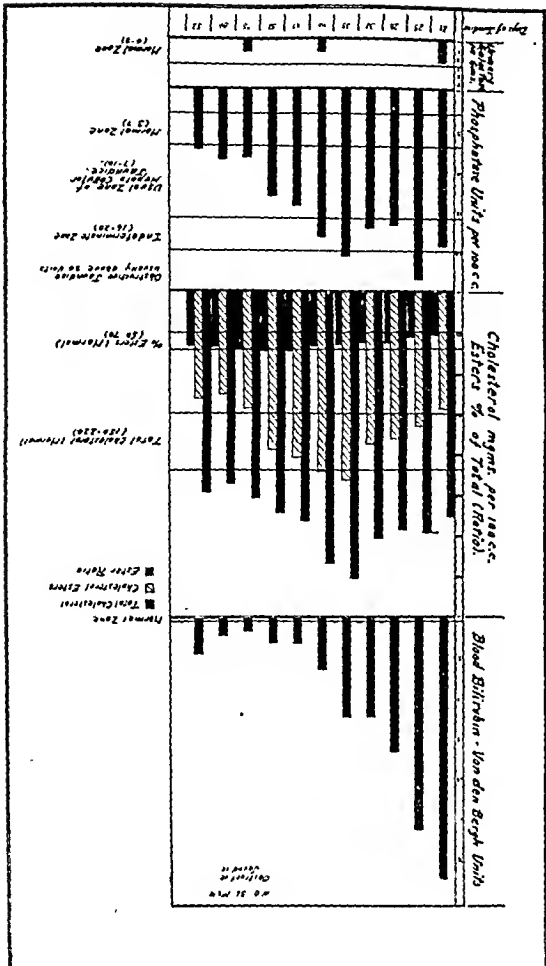
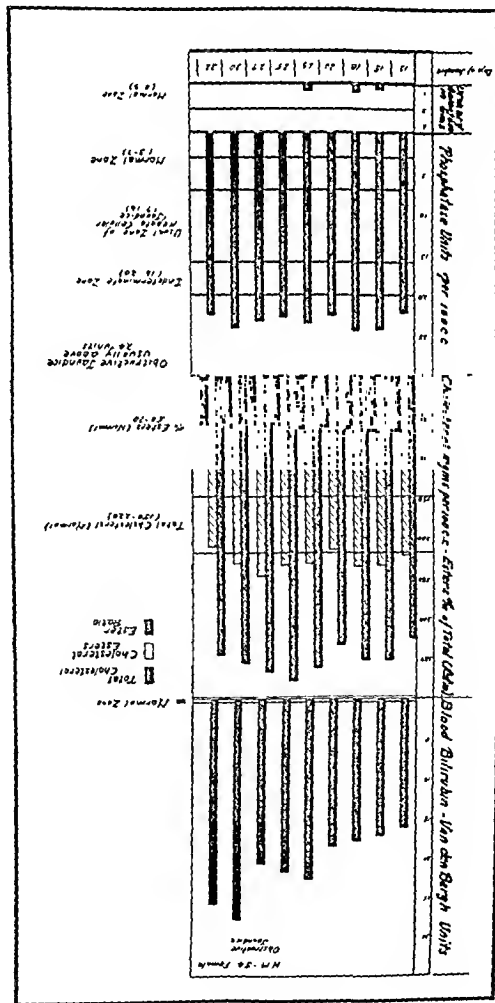
bilirubin. In this instance the return of the galactose test to normal more closely parallels the rise in cholesterol esters.

CHOLESTEROL PARTITION

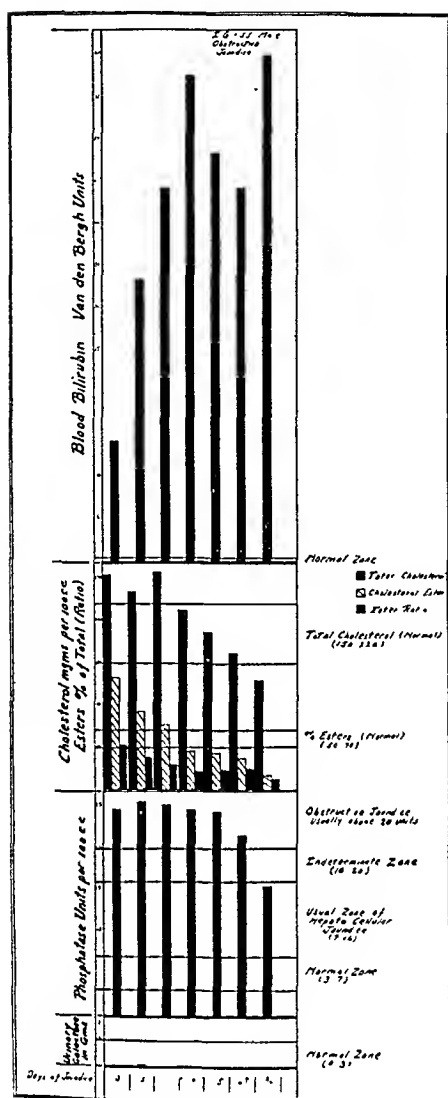
Although Austin Flint, Jr. (15), as early as 1862 described "a new excretory function of the liver which consisted in removing cholesterol from the blood" and attempted to utilize the fate of blood cholesterol to differentiate between obstructive jaundice and suppression of bile, it was not until better methods of cholesterol analysis had been developed that the necessary impetus for detailed studies of cholesterol metabolism was achieved. In the present study, we are concerned only as it relates to jaundice. Thannhauser (16) who in our opinion offers the most workable hypothesis, says the liver is the main excretory organ of cholesterol and regulates the relative content of the blood in both cholesterol and cholesterol ester. Further, Thannhauser and Schaber (17) attributed the drop in cholesterol ester in hepatic cell damage to a disturbance in liver synthesis and hydrolysis of cholesterol esters. They consider this reversible reaction dependent upon the enzymes of the liver cells, which are disturbed in diffuse parenchymatous lesions. Sperry

and graphically show what we have previously said about the importance of doing this test early in the jaundice. Thus in Cases 1, 2, 3 and 10, all cases of obstruction, we find readings below 3 grams. Unfortunately, in Cases 3 and 10 we did not obtain galactose readings at the time diffuse liver damage supervened. An excretion of over 3 grams at these times would have been the expected result. Cases 4, 5, 7 and 8 show the typical results obtained with the galactose tolerance test in toxic jaundice. Case 6 illustrates what may happen if the galactose tolerance test is done when liver cell recovery has already set in, although the jaundice is still quite marked. The low galactose output on the 10th day of jaundice if interpreted independently could readily be taken as a failure of the test. However, both the rapidly falling blood bilirubin and rising cholesterol esters indicate that the recovery and rising cholesterol esters indicate that the recovery, too, that liver cell recovery, as indicated by a return of galactose utilization to normal, varies in different cases. Thus in Case 4, the excretion of galactose drops only gradually in comparison with the drop in blood

Case 1



Case 2



Case 3

jaundice may be and then consider deviations and their explanations.

In uncomplicated obstructive jaundice, the expected result is hypercholesterolemia with the maintenance of a normal cholesterol ester ratio of 50% to 70% of the total cholesterol.

Case 1, a carcinoma of the head of the pancreas, was followed for a little over a month before operation. The total cholesterol ranged from 325 to 375 mgms. per 100 cc. but was accompanied by a proportionate rise in cholesterol ester so that the ratio is maintained between 50% and 70%.

Hypercholesterolemia with obstructive lesions of the biliary tract was observed by Austin Flint, Jr. (15), seventy-five years ago. Rothschild and Felsen (23) as well as Stepp (24) noted a direct relationship between the degree of jaundice and the cholesterolemia in pure, uncomplicated cases of obstructive jaundice. This is usually true when the obstruction is stationary. However, in an uncomplicated obstruction in which the obstruction decreases, this relationship does not hold.

Case 2 illustrates this feature. An uncomplicated duct obstruction due to a stone which was relieved spontaneously, showed a rising blood cholesterol and esters when the quantitative van den Bergh was dropping rapidly. A similar change is frequently seen in the recovery period from toxic hepatitis as well.

Our findings corroborate those of Epstein and Greenspan (25) who failed to see an absolute parallelism between the degree of hyperbilirubinemia and the hypercholesterolemia in their group of obstructive jaundice.

Rothschild and Felsen (23) recognized that an infection altered the direct relationship between the increase in cholesterol and the degree of jaundice. This was recently stressed by Wilkinson (26) and is illustrated by Case 3. In this instance, there was again a common duct stone obstruction, but infection and high fever had supervened. Here we saw a rapidly rising blood bilirubin accompanied by a falling total cholesterol and an even more rapid decrease of cholesterol esters so that the ratio was considerably below normal. Such a rising blood bilirubin and dropping cholesterol and esters are usually of serious prognostic import, especially in cases of obstructive jaundice. In this instance the patient died 2 days after the last group of readings were obtained. (See Case 10 in which instance the patient also died).

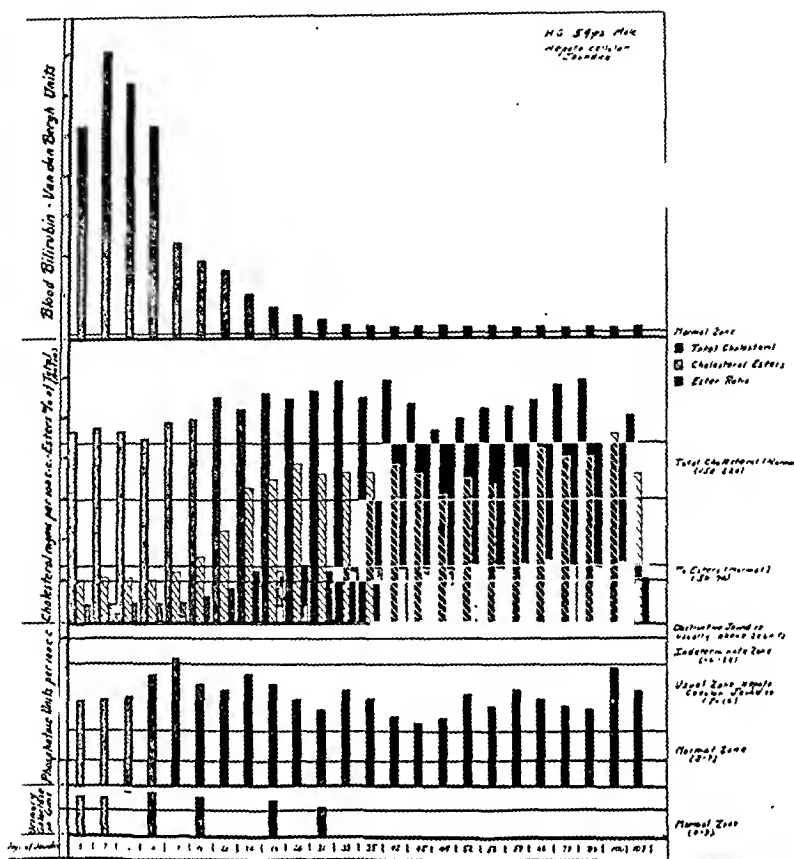
Our data in conformity with those of Epstein and Greenspan (25) do not support the opinion of Burger and Habs (20), Gardner and Gainsborough (22) and Stroebe (27) that the hypercholesterolemia in obstructive jaundice is caused mainly by an increase in free cholesterol and that ester is not proportionately raised. Their interpretation that this results from the absence of bile in the intestines which in turn is responsible for a reduction of cholesterol ester absorption by the intestine, is also not supported by experimental evidence. Hawkins and Wright (28) found the absence of bile in the intestines and a faulty absorption of fat in biliary fistula dogs did not result in a dissociation of the ester ratio. Furthermore, Rosztochy (29) in rabbits and Stern and Suchantke (21) in dogs found an increase in both free and ester cholesterol after common duct ligation.

In toxic hepatitis, the typical picture is a normal or moderately increased total blood cholesterol with a decrease in esters which results in a lowered ratio. Here

(18), Salomon (19), Burger and Habs (20), and others believe that the intestinal mucosa is the main avenue of excretion for cholesterol. Burger and Habs (20), Stern and Suchantke (21) and Gardner and Gainsborough (22) would rather consider the drop in esters the result of the failure of fat absorption. This necessitates the deesterization of combined cholesterol in the plasma to permit the utilization of the fatty acid.

Since the level of blood cholesterol is influenced by the variations in the functions of the pituitary, thyroid, gonads, pancreas, and adrenals as well as by many conditions not directly related to the function of these glands, the application of cholesterol studies to the problem of general liver disease would be subject to many limitations. However, restricting its use to the changes produced in jaundice, the study of the cholesterol partition is a valuable diagnostic aid.

To simplify discussion let us consider what the expected results in uncomplicated obstructive and toxic



Case 4

a divergence between the intensity of the jaundice and the concentration of blood cholesterol is the rule. Although Feigl (30) first observed low cholesterol ester values in acute yellow atrophy, its clinical significance was not appreciated until Thannhauser and Schaber (17) eight years later recognized that it represented a disturbance in the ability of the liver to regulate the level of the free and combined cholesterol of the blood. Their findings have been confirmed by a number of investigators and especially by Epstein (31). A typical result in toxic hepatitis is seen in Case 4. Here with the intense icterus, the normal total cholesterol is accompanied by a marked depression of the esters so that the ester ratio was reduced to less than half of normal. This case also illustrates what is commonly seen in recovery in toxic hepatitis. There is usually a rise in both total cholesterol and esters often to above normal limits with a later return to normal (see Cases 5 and 6).

In our experience, a rise in esters was accompanied by a fall in blood bilirubin. While, as previously noted, a divergence between the total cholesterol and the intensity of jaundice was the rule, a close inverse relationship of changes in blood bilirubin and cholesterol ester ratio is usually seen. Thus, in the course of toxic hepatitis an increase in jaundice is usually accompanied by a decrease in ester ratio, while the reverse is true in the recovery period. The rise in ester ratio

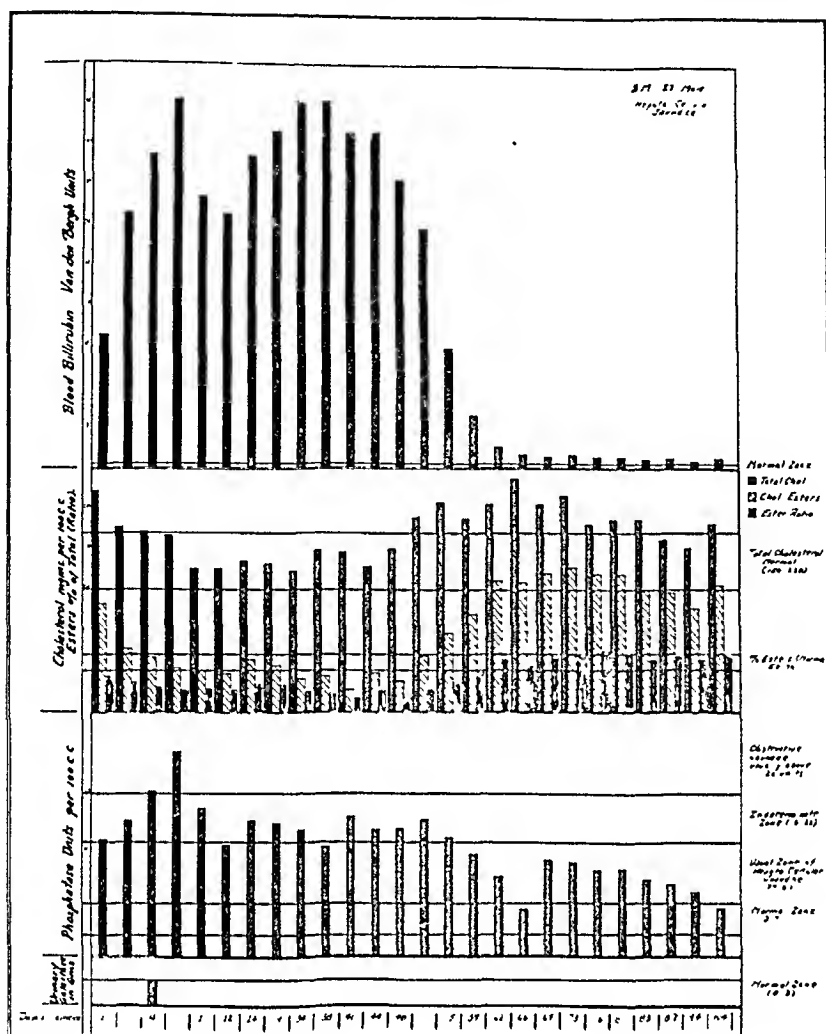
has been very useful in establishing the recovery period in toxic hepatitis. This is well illustrated in Case 5.

In mild cases of toxic hepatitis cholesterol esters may fail to show a diagnostic drop at any period of the jaundice. Case 7 is illustrative of such an instance. Further, it shows in addition to a hypercholesterolemia a most striking rise in cholesterol at the second examination on the 10th day of jaundice in the recovery period. There was, too, a sharp rise in esters. This may represent an exaggerated rise in the recovery period previously mentioned, but we have never seen anything so sharp before. Occasionally, too, we saw results which we were unable to explain. Thus, in Case 8, a case of toxic hepatitis, the hypercholesterolemia and normal ester ratio on the 3rd day of jaundice were followed on the 5th day by a very sharp drop in both, especially the esters, despite the fact that recovery was taking place.

In Case 9 we had an opportunity to follow the course of the jaundice in two attacks of toxic hepatitis. In both, the characteristic changes for cholesterol and esters occurred.

PHOSPHATASE

Roberts (1) in 1930 was the first to report an increase in plasma phosphatase in jaundice. Three years later he (32) reported a series of 52 cases which convinced him that the phosphatase level in the blood offered a means of differentiating between obstruc-



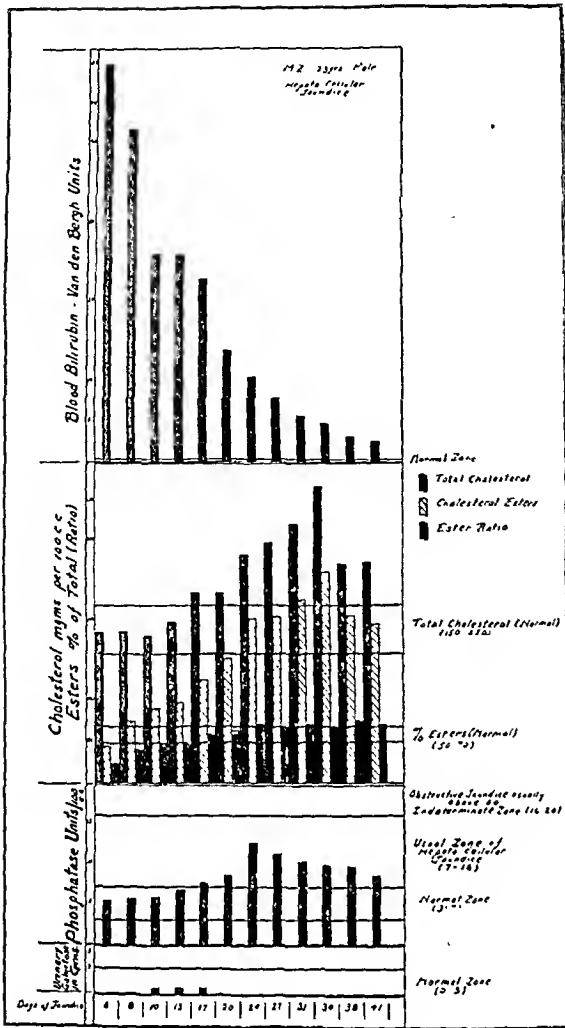
Case 5

tive and toxic jaundice. Since then many reports on the test have appeared: with some investigators as thoroughly convinced as Roberts of its value; with others just as certain that it is without merit. Allowing that both groups of results are equally reliable, one may assume from experience with liver function tests that both groups of investigators are correct, within certain limits. Both, however, fail to take cognizance of the frequency with which obstructive jaundice has a superimposed toxic factor as well as the commonly occurring phase of bile canalicular obstruction in toxic hepatitis. These superimposed phases may diminish, neutralize, or completely conceal the effect produced by the basic type of the jaundice actually present.

It is our belief that no test concerned with changes in liver activity incident to jaundice can ever be properly interpreted without a knowledge of the limitations thrust upon it by the liver itself. These limitations for the phosphatase have not as yet been established. The test is further beset because there is no single accepted technique, a fact that makes reported results not entirely comparable. Furthermore,

the higher and variable normal level in the young further complicates the interpretation of phosphatase readings in jaundice in this group.

Roberts (32) found that in jaundice due to mechanical obstruction of the bile ducts the blood phosphatase showed a striking increase (10.9 to 22.9 units); in jaundice of the toxic or infective type the figures were either normal or slightly raised (3.7 to 8.9 units, except for one case of catarrhal jaundice in a child). Meranze and Meranze (33) in an earlier report from their laboratory, using the Kay Roberts method, found figures that are identical with those obtained by Roberts (32). In this series, using the Kay Roberts method, we obtained consistently higher readings. With the results we have obtained, the limits for the toxic range reported by Roberts must be raised if the readings are to be of any value. These results fit in best with those reported by Freda K. Herbert (34) and have led us to consider readings below 16 units as due to toxic hepatitis; figures above 20 units to obstructive jaundice, and those between 16 and 20 units to belong in the indeterminate zone. The interpretation of all figures, however, is dependent not only



Case 6

upon the clinical picture, but upon the results of the test repeated at 2 to 3 day intervals over a period of a week.

Since Meranze and Meranze have obtained lower readings with the same method, and frequently on the same sample of serum in which higher readings were obtained by us, we believe it extremely important for the present that each laboratory using the phosphatase test establish its own limitations for the range of toxic hepatitis until such time as there is a standardized method. Otherwise, a test which appears to have some usefulness in the differentiation of toxic and obstructive jaundice may fall into disrepute.

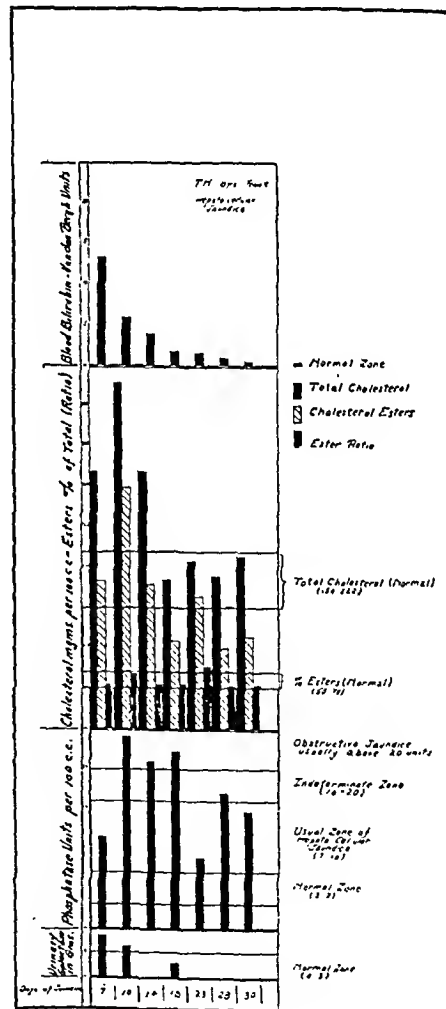
In general, reported readings have been higher in the obstructive jaundice than in the toxic group. Some, however, have seen as wide a range in both groups. Thus Greene, Shattuck and Kaplowitz (35) have reported figures for plasma phosphatase in obstructive jaundice ranging from 11.6 to 63.2 units, and in hepatitis from 8.4 to 72.2 units. Fiessinger and Boyer (36) likewise found that a considerable increase in blood phosphatase was not limited to the obstructive form

of jaundice. Cantarow (37) has reported similar findings. Morris and Peden (38) found overlapping of the values in the two groups of jaundice—a result similar to that reported by Anderson (39).

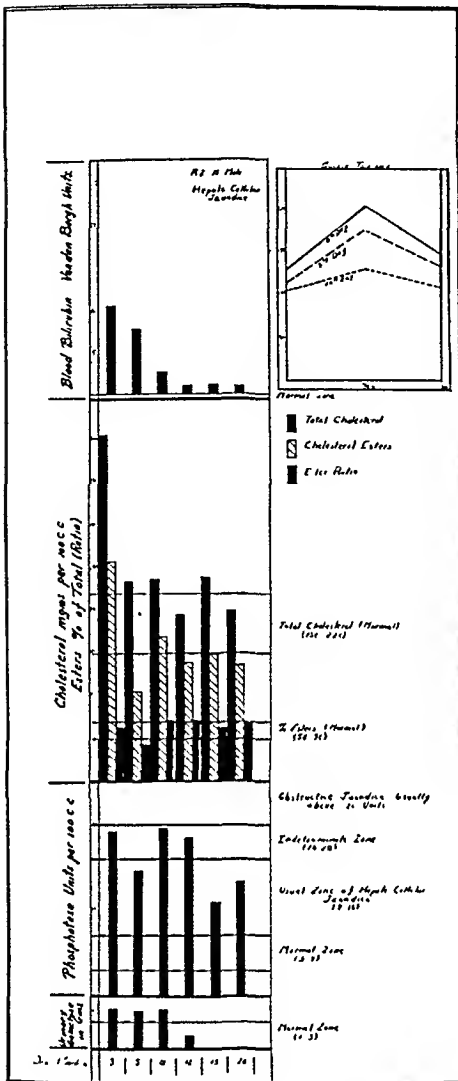
Herbert (34) in her data shows an association of high phosphatase figures with obstructive jaundice, but indicates that in a certain proportion of toxic or infective cases moderate rises, or rarely, marked rises in the plasma phosphatase can occur. Thus in the obstructive group she found that the majority of values were above 20 units while only 2 of 22 cases of toxic jaundice were above this figure. This in general is more nearly in accord with our results.

One must remember that here, too, diffuse hepatic damage in obstruction (Cases 3 and 10) can cause a drop in phosphatase in spite of a rising icterus while the obstructive phase in toxic hepatitis may be so marked as to produce readings even in adults in the indeterminate zone (Cases 4 and 5) and at times actually above 20 units (Case 5).

As previously pointed out, the higher normal figures seen in the young may be responsible for the usual



Case 7



Case 8

higher phosphatase figures seen in toxic hepatitis in young people.

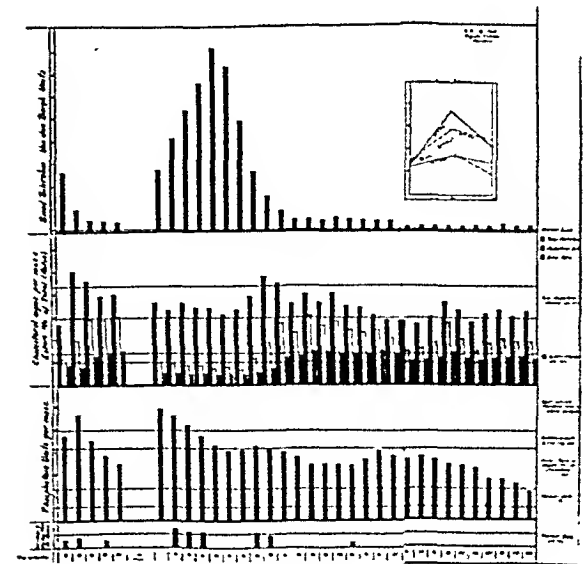
This facile explanation must not be accepted too readily because, as indicated by Case 9, when followed long enough to establish complete recovery, we find that the normal phosphatase for this child of 15 years was in the normal adult range. It is our impression that phosphatase readings in toxic hepatitis run higher in children than in the adult and to a degree that cannot be accounted for by the usually higher normal phosphatase reading alone. For this reason especially do we believe it important not to attempt at present to make the toxic hepatitis zone too narrow. Furthermore, since it has not been established at which age the phosphatase drops to adult levels; whether this is a sudden or gradual process; and whether it occurs at the same time for all individuals, more flexible standards at this time will certainly be more useful in establishing the value of the test.

The mechanism for the larger increase of phosphatase in obstructive jaundice and the usual slight increase in toxic jaundice is as yet not clearly explained.

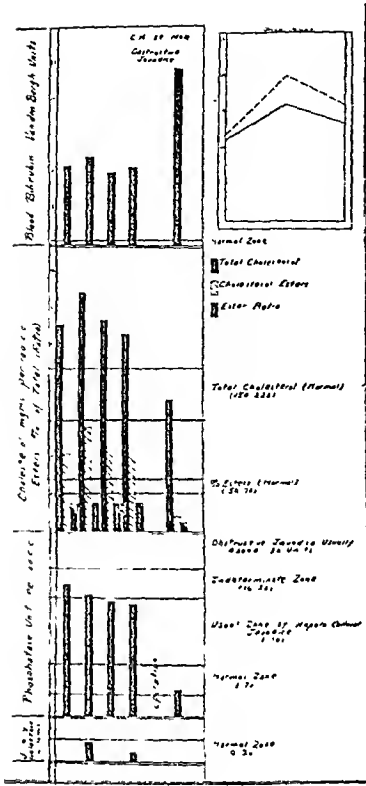
The rise in the former type has been attributed to the re-absorption into the blood stream of bile which has a high phosphatase content. General clinical experience and the results of experimental obstructive jaundice appear to support the view that the liver acts as an organ for excretion of phosphatase, although Austoni and Coggi (40) and more recently Morris and Peden (38) have suggested that the height of the blood phosphatase in jaundice depends upon an impaired supply of calcium to the bones incident to a defective absorption of calcium in jaundice. This factor remains to be determined. Although Bodansky and Jaffe (41) felt that the liver was an important source of plasma phosphatase, more recent experiments of Armstrong and Banting (42) clearly indicate that the liver does not contribute any of this enzyme. They are of the opinion that the bones constitute the sole source of serum phosphatase. This is in accord with views voiced by Herbert (34) and by Anderson (39).

While it would be helpful to visualize an increase of blood phosphatase in jaundice as an expression of obstruction whether canalicular or extrahepatic as suggested in the views of Herbert (34) and of Anderson (39), our present serial studies do not permit such an interpretation. Thus Case 3, an obstructive jaundice at the thirty day period when diffuse hepatic damage was superimposed, had a sharp drop in phosphatase in spite of the sharp rise in jaundice. Case 10 illustrates the same result. Not infrequently, too, one sees a definite rise of phosphatase in the recovery period of toxic hepatitis. Cases 4, 6, 7, and 8 in the light of the blood bilirubin curve could hardly be attributed to any increase in obstruction. It is also difficult to attribute those changes to changes in calcium absorption at those times. An adequate explanation for all the changes in the blood phosphatase in jaundice is still to be found.

Illustrated in this paper are 148 readings of phosphatase in jaundice. Thirty six in obstructive jaundice and one hundred and twelve in toxic hepatitis. Using the standards employed in this paper, nineteen of the 36 readings gave evidence of the obstructive nature of



Case 9



Case 10

the jaundice (i.e. readings above 20 units). Of the remaining seventeen readings, six fell in the indeterminate zone between sixteen and twenty units while eleven were below sixteen. It must be considered, however, that of these eleven readings, five were taken when the bilirubin level was near normal in the recovery period from a stone obstruction. Three represented low phosphatase readings incident to superimposed hepatitis in obstruction. In the pure obstructive group, then, the phosphatase reading was definitely informative.

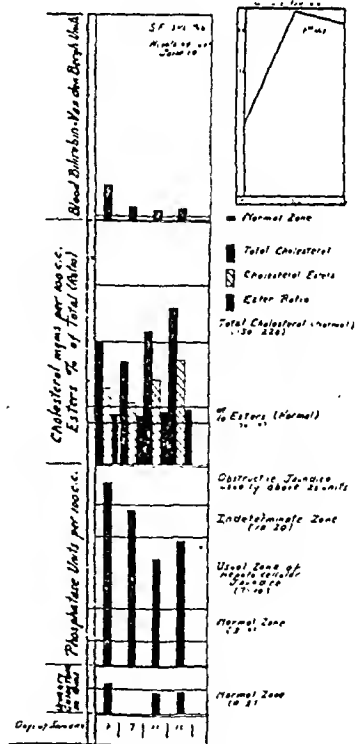
The toxic jaundice group, while represented by 112 readings, only 70 can actually be considered because the remaining forty-two readings were taken in practically the recovered period. These would naturally, fall in the low level zone. Of the 70 readings when definite jaundice was still present, 38 were below 16 units, 21 between 16 and 20 units, and 11 above 20 units. It must, however, be indicated that of the 21 between 16 and 20 units, ten instances occurred in children 15 years and younger, and 11 occurred in adults, and of those readings above 20 units, 8 occurred in children and only 2 in adults. Summarizing, readings above 20 units obtained under the conditions employed in this study are in favor of obstructive jaundice; readings below 16 units, provided one can rule out the recovery period of an obstructive jaundice, are in favor of a toxic hepatitis. In obstructive jaundice due to superimposed infection low phosphatase readings may be obtained and in the obstructive phase of toxic hepatitis readings above 16 and even above 20 units may result. The latter, however, occurring most often in the first

two decades of life. The impression is that although the normal blood phosphatase in young people may be on the average higher than in adults, there is apart from this a tendency to higher phosphatase values in toxic jaundice in the young as compared with adults.

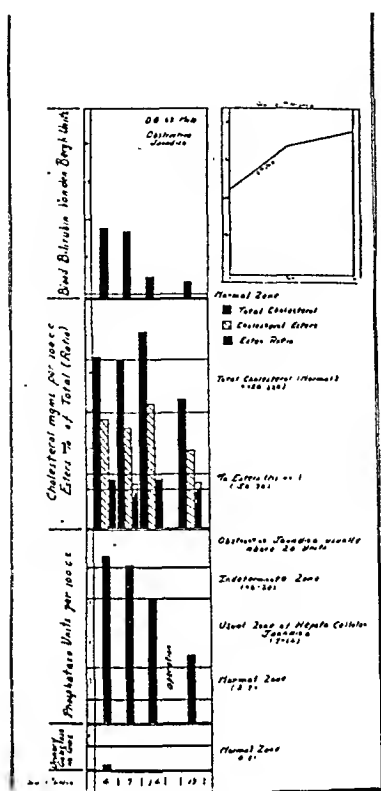
GLUCOSE TOLERANCE TEST

Recently Jacobi (4) (43) suggested that the glucose tolerance test be used in the differentiation of toxic and obstructive jaundice. The many factors involved in the blood sugar response to a test load make us doubt whether the application of the glucose tolerance test can be so closely circumscribed. Jacobi, however, reported some striking differences in the results obtained in the two types of jaundice. We have, therefore, used this test in the study of our cases of jaundice. While our experience is as yet not extensive enough to permit the expression of an opinion regarding its value, our results have thus far been similar to his. While we believe a much larger experience will be necessary to establish its usefulness and especially its limitations, we do think it worthy of further investigation.

Jacobi described for toxic jaundice two types of curves following the ingestion of 100 grams of glucose. He recommends taking fasting blood sugars: one forty-five minutes after the ingestion of the glucose and one at two hours. In the flat curve, the rise in blood sugar is very slight throughout the period following the intake of the glucose. This type is exemplified especially well in Case 8. The second type shows a low fasting blood sugar followed by an early high rise and a subsequent fall to the normal or fasting level at the end of the 2nd hour period. Case 9 on the



Case 11



Case 12

14th day of jaundice gave a typical curve. If the test is repeated often enough in the course of the jaundice, both types of curves are found, as illustrated in Case 9.

In common duct block by stone stricture or suppuration, Jacobi described a sugar tolerance response characterized by a gradually ascending curve. Beginning with either a normal or elevated blood sugar, the curve rises steadily so that the two hour figure is always considerably higher than that of the fasting blood sugar. This type was seen typically in a case of common duct stone obstruction in Case 12. We have, however, encountered what would have to be considered typical obstructive curves in toxic jaundice as shown in Chart II and have seen the toxic jaundice type of curve in proven common duct obstruction as shown in Case 10. The latter results are not offered as evidence denying any value to the glucose tolerance test in jaundice. Rather, we wish to draw attention to the fact that many cases of jaundice will have to be studied in which the test is repeated frequently during the jaundice in order to determine what limitations the changing picture of jaundice will produce in the type of glucose tolerance curve.

SUMMARY

The use of any liver function test in jaundice should not be limited to a single determination. Furthermore, a combination of tests whose interpretation and limitations are reasonably well understood would certainly lessen the chance for error. It is our belief that mistakes in diagnosis between obstructive and toxic jaundice could be practically eliminated if the group of tests employed in this report are repeated approxi-

mately three times in the course of a week during any period of jaundice. By evaluating the results obtained with the clinical picture, one may with assurance determine the type of jaundice present. Furthermore, the various tests are influenced somewhat differently by the obstructive phase in toxic jaundice, and a superimposed toxic factor in obstructive jaundice. In general the results of the galactose tolerance test appear to parallel those obtained by a study of the cholesterol partition.

In some cases, Case 6 and Case 9, normal levels of galactose were reached before the return of the ester ratio to normal. In such cases the cholesterol partition seems to be the more sensitive of the two. In other instances, Case 4, the reverse appears to be the case. In still other instances, Case 7, 8, and 11 positive galactose tolerance readings were obtained when the cholesterol partition was entirely normal. The obstructive phase in toxic hepatitis does not appear materially to affect either the galactose tolerance or cholesterol partition while the phosphatase may at such times reach the indeterminate zone or even obstructive levels. This is especially important in adults (Case 5). On the other hand, both the galactose tolerance and the cholesterol partition are more readily affected than the phosphatase level by toxic changes superimposed upon obstructive jaundice. It has been our experience that a sharp drop in phosphatase level which accompanies a sharp drop in total cholesterol and esters in the presence of a rising blood bilirubin is of very serious import especially if occurring in obstructive jaundice (Cases 3 and 10) when it usually spells a fatal outcome. The exact value of the glucose tolerance test in this problem must be established by further work.

For those who may not have available fully equipped laboratories to carry out the elaborate chemical processes involved in the cholesterol and phosphatase determinations, the simple galactose tolerance test, if done properly early in jaundice and interpreted on the basis of the criteria laid down, still remains the most reliable single laboratory test in the differentiation of toxic and obstructive jaundice.

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DISCUSSION

DR. HENRY L. BOCKUS (Philadelphia, Pa.): Mr. President, Ladies and Gentlemen: I was disappointed in Dr. Shay's paper because I was hoping that he would give me some opportunity to take exception to what he had to say, as I had no opportunity to read his paper before he presented it.

I think all of us here who have had a fairly wide clinical experience, know that there is a small group of cases of jaundice in which it is rather difficult to make a diagnosis without the use of certain laboratory methods. Clinical methods are good enough in possibly 75 per cent of the cases, but there are a considerable number in which we need other help.

I should like particularly to congratulate Dr. Shay for the manner in which he went about this study. I think the ability to visualize the results these tests carried out on a small group of cases from the beginning to the end of the course of jaundice means a great deal more than do group statistics attempting to state how valuable the galactose test is in a group of one hundred and fifty cases, or how valuable the hippuric acid test is, or any other single test.

Anyone who knows anything about liver physiology and jaundice, knows that the situation varies day by day and week by week, and it is only by careful measurement by a number of different methods, done at the same time, that one can actually arrive at a definite conclusion concerning the state of liver cell function and destruction at that particular time.

I have had very little sympathy with people who publish papers on large groups of cases without drawing attention to that fact.

Of course, all of us do not have a private laboratory at our disposal. Many of us cannot do all these tests on any given case, but I think you will gather from Dr. Shay's statistics here that if you select the galactose test early in the course and follow it through, and the cholesterol partition, and possibly a glucose tolerance test, you have information that is rather reliable in the great majority of cases.

I agree with Dr. Shay that the phosphatase test needs a little more study before its value is established in the differential diagnosis of jaundice.

I should like very much to have the President invite Dr. Rothman to discuss that phase of the subject, if he is here, because he has had a tremendous experience with it.

I should like to close by stating that I feel that this contribution that Dr. Shay has made has done more to clarify the question of differential diagnosis from the laboratory standpoint in these two types of jaundice, than perhaps any paper I have read.

(Dr. Rothman was called upon but was not present).

DR. HARRY SHAY (Philadelphia, Pa.): Mr President, I only wish to thank Dr. Bockus for his discussion. Since we are in complete agreement there is nothing to add.

A Proved Case of Recovery from Fatty Metamorphosis of the Liver After Treatment with Lipocaic*

By

DAVID H. ROSENBERG, M.D.

CHICAGO, ILLINOIS

IN 1924, Fisher (1), and Allan, Bowie, Macleod and Robinson (2), observed that depancreatized dogs treated with sufficient insulin to control the diabetic symptoms, developed signs of hepatic insufficiency, became insulin-sensitive, and died in a state of hypoglycemia within one to eight months. Necropsy studies revealed a marked fatty infiltration and degeneration of the liver as the principal or sole abnormality. By the addition of raw pancreas to the diet, Allan and his co-workers were able to prevent such hepatic changes and to permit survival for a long time. These observations have since been confirmed repeatedly by different investigators (3, 4, 5, 6). Accompanying the enormous accumulation of fat in the liver (consisting mainly of triglycerides [neutral fat]) (7), Chaikoff and Kaplan (8) reported a decrease in the whole blood lipids and, in most animals, a disappearance of the cholesterol esters.

The nature of the essential factor in raw pancreas has been the subject of extensive research. That this substance is not supplied by the pancreatic enzymes was indicated by the work of Hershey and Soskin (3) and others, and now seems conclusively demonstrated by the experiments of Prohaska, Dragstedt and Harms (6), who were unable to prevent the hepatic changes by the feeding of adequate amounts of fresh pancreatic juice. Hershey (9) and Hershey and Soskin (3) found that the daily administration of egg yolk lecithin prevents as well as cures the fatty metamorphosis of the liver, as shown both histologically and chemically, and permits survival of the animal for considerable periods of time. Best and his co-workers (5) confirmed this work, and found choline to be the effective component in lecithin. Betaine, similar to choline chemically, had an analogous effect (5c). Recently, Dragstedt, Prohaska and Harms (10) prepared a fat free alcoholic extract of beef pancreas ("lipocaic") which, when fed to depancreatized dogs, proved as effective orally as either raw pancreas, lecithin or choline, and which they believe to be a "fat metabolizing hormone," concerned in the normal transport and utilization of fat.

The application of these experimental observations to therapeutics in man was attempted by Judd, Kepler and Rynearson (11), who administered choline and betaine to two patients with fatty metamorphosis of the liver (biopsy) accompanied by hypoglycemia, but no beneficial effects were observed. Dragstedt and his co-workers (12) exhibited lipocaic to patients manifesting diabetes mellitus in association with hepatomegaly and noted a decrease in the size of the liver. A similar effect was observed by Grayzel and Radwin (12 a) in three cases of juvenile diabetes mellitus

treated with a pancreatic extract prepared according to the method of Dragstedt et al. In a presumptive case of fatty metamorphosis of the liver (? portal cirrhosis), Snell and Comfort (13) reported a rapid decrease in the size of the liver and an improvement in the hepatic function during the first twelve days of lipocaic therapy. Their patient had also received an increased carbohydrate diet both before and during such therapy. In no instance, however, have the effects of this substance been observed in a proved human case of fatty metamorphosis of the liver.

We have had the opportunity of administering lipocaic to a patient with marked fatty metamorphosis of the liver associated with diabetes mellitus, correlating the clinical observations with the results of liver function and glucose tolerance tests and with the gross and histologic appearance of the liver both before and after treatment. The findings are so striking as to merit this report.

CASE REPORT

J. S., a white female, aged 59, a housewife, was admitted to the Mandel Clinic on March 3, 1937, complaining of weakness and shortness of breath. For 4-5 years, she had noted a sharp, sticking pain over her heart, which pain appeared when she became emotionally upset or after working hard, and which was accompanied by dyspnoea. Three months ago, dyspnoea became more noticeable following exertion, and a rather striking degree of weakness was evident, both of which symptoms had persisted. She had gained 20 pounds (9.1 Kg.) in weight during the last six months without apparent increase in food intake.

Past History: During her first pregnancy, at the age of 23, she had gained 30 pounds (13.6 Kg.) in weight and noted the development of facial hirsutism. In the subsequent eight years, she gained an additional 20 pounds (9.1 Kg.), her weight remaining constant thereafter, until the onset of the present illness. In 1933, a hysterectomy was performed for the removal of uterine fibroids. The remainder of the history was non-contributory.

Physical examination revealed a rather obese, well developed individual who did not appear acutely ill. Dyspnoea and orthopnoea were conspicuously absent. There was an excessive growth of hair on the face and to a lesser extent on the forearms, lower extremities and lower abdomen; a sparse growth was present on the areola of the breasts. The heart was slightly enlarged to the left. A short, soft, blowing, systolic murmur was audible at the apex, and was transmitted to the lower sternum; a similar murmur was heard at the first and second right interspaces. The pulse was 90 per minute, regular and of good quality. A marked diastasis recti and a slight umbilical hernia were present. The liver edge descended 10 cm. below the costal margin in the mid-clavicular line on inspiration. It was smooth, sharp, of increased consistency and moderately tender on pressure. Only slight pretibial pitting edema was noted. The blood pressure was 185 systolic and 95 diastolic. No other physical abnormalities were found at this time. The urine was normal. A two meter film of the heart and aorta revealed a slightly in-

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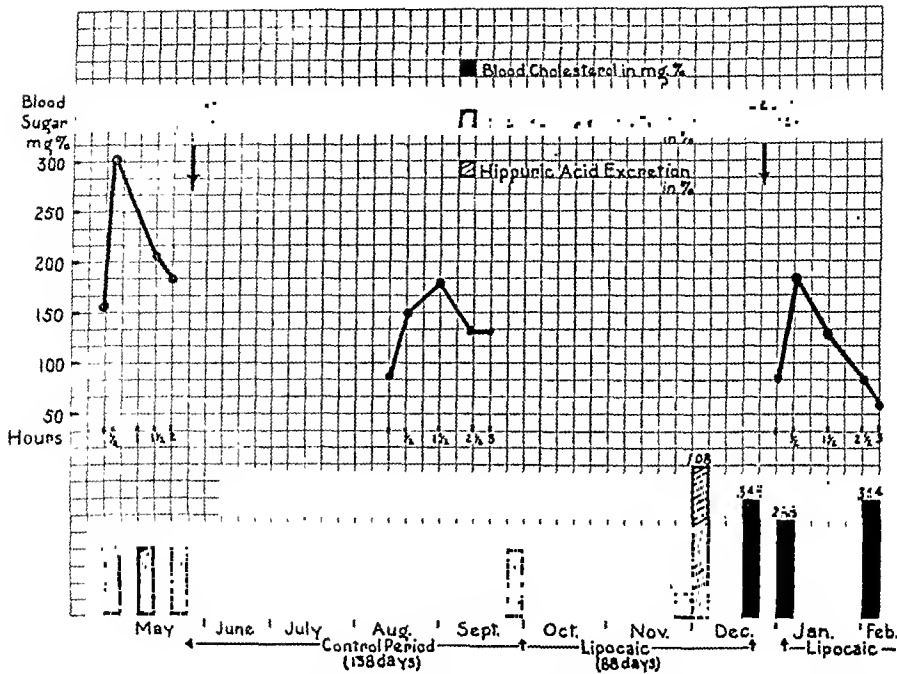


Chart 1. Showing the effect of lipocaic upon the function of the liver and upon the blood cholesterol. Note the normal response to the bromsulphalein, hippuric acid and glucose tolerance tests and the rise in blood cholesterol after treatment. (Normal fasting blood sugar according to method employed: 60-95 mg. per 100 cc. blood).

increased cardiothoracic ratio (14.3/27.7 cm.), a normal cardiac outline and a calcific plaque in the aortic arch. Having shown no response to digitalis and rest after a period of four weeks, she was admitted to the Michael Reese Hospital on April 17, 1937, for observation (service of Dr. Sidney Strauss). Her temperature was 98.6 F.; pulse 90 and respirations 18 per minute. Weight 193 pounds (87.8 Kg.). Physical examination elicited the same findings as recorded above. The urine was negative except for a trace of albumin. Blood examination: Hemoglobin, 65 per cent; erythrocytes, 4.1 million; leucocytes, 7600; differential formula, normal. Sugar, 97 mg. per 100 cc. blood (normal, 60-95 mg.); non-protein nitrogen, 38 mg.; cholesterol, 176 mg. Wassermann and Kahn tests, negative. Electrocardiogram: Rate 88. P-R interval 0.16 sec. QRS up in leads 1 and 2, small and slurred in lead 3. S-T, and, are slightly depressed. T is inverted in leads 1 and 2, and inverted and small in lead 3. QRS mainly up. Sinus rhythm.

Tentative diagnosis: 1. Obesity. 2. Hypertension. 3. Arteriosclerotic heart disease with slight cardiac hypertrophy; arteriosclerosis of the aorta. Sinus rhythm. 4. Secondary hypochromic anemia. 5. Exclude ovarian, adrenal and pituitary disease as the cause of the hirsutism.

The therapy consisted of bed rest, digitalis and an 800 calorie diet. On the third day of admission, her pulse rate was 80 per minute. The visual fields were normal. Roentgenograms of the sella turcica were normal. A fasting blood sugar of 190 mg. was obtained on the fifth day. May 3, a glucose tolerance test,* injecting 50 cc. of 50 per cent glucose intravenously, yielded the following results: Fasting control, 158 mg.; after 15 minutes, 303 mg.; 1 1/2 hours, 202 mg.; 2 hours, 181 mg. (Chart 1). On the same day the blood calcium was 10 mg. per 100 cc. blood; phosphorus 1.3 mg. (normal, 2-3 mg.).

Although the weakness was less marked, her general

condition after 2 1/2 weeks had shown little if any improvement despite the fall in blood pressure to 150 systolic and 80 diastolic, a pulse rate of 72 per minute and a loss of 20 pounds (9.1 Kg.) in weight. The liver had not receded in size, and was still tender on pressure and of increased consistency. It seemed apparent at this time, that the disorder of the liver was unrelated to the cardiac state, and that a diagnosis of hepatic cirrhosis was more tenable.

On May 5, the icterus index was 5; van den Bergh test: direct, faint delayed positive; indirect, faint immediate positive. May 7, the hippuric acid test of liver function revealed an excretion of only 49 per cent of normal (1.48 Gm. in terms of benzoic acid).† Pneumoperitoneum disclosed a globular mass, believed to be an arrhenoblastoma of the ovary, located in the right side of the pelvic cavity. For the first time, a glycosuria was detected on this day, the maximum daily excretion prior to operation being 6 Gm. On May 9 the bromsulphalein test revealed 20 per cent retention at the end of 30 minutes (Chart 1). The blood sugar was 173 mg.; weight, 177 pounds (80.5 Kg.).

A laparotomy was performed on May 12 by Dr. M. L. Leventhal, and a slightly enlarged, freely movable, right ovary (fibroma theca cellulare [Dr. O. Saphir]) was removed. The left ovary was shrivelled, small and hard. The liver was enlarged and appeared grossly fatty, yellowish and mottled. The gall bladder was distended and contained a palpable, freely movable gall stone. Upon request, a section of the liver was removed for biopsy and fixed in Zenker's solution.

Histologic examination (Figs. 1 A and B): The architecture of the liver is barely recognizable. Throughout most of the section, the liver cells are swollen and the cytoplasm is clear, filled with large round vacuoles and does not take the stain; the nuclei either do not stain or are displaced to the periphery of the cells, presenting a "signet-ring" appearance. In a few areas, more normal appearing liver cords are seen, the cells of which are

*All glucose tolerance tests were performed by Dr. Rachmiel Levine of the Department of Metabolism.

†Normal, 3.0 Gm. Limits of normal—85-110% excretion (14).

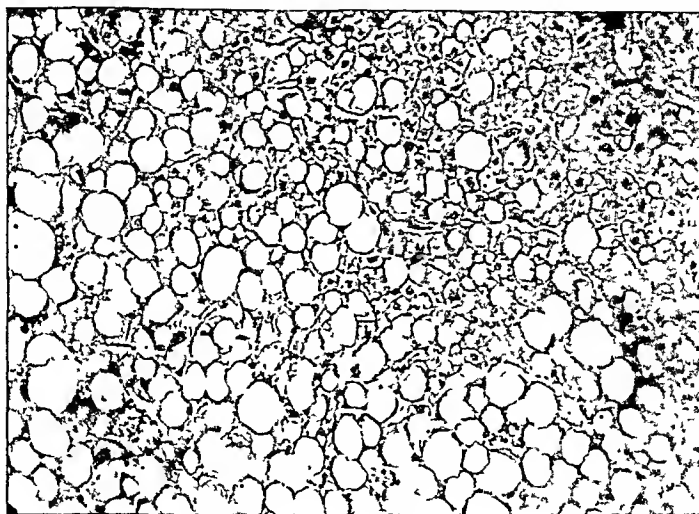


Fig. 1A

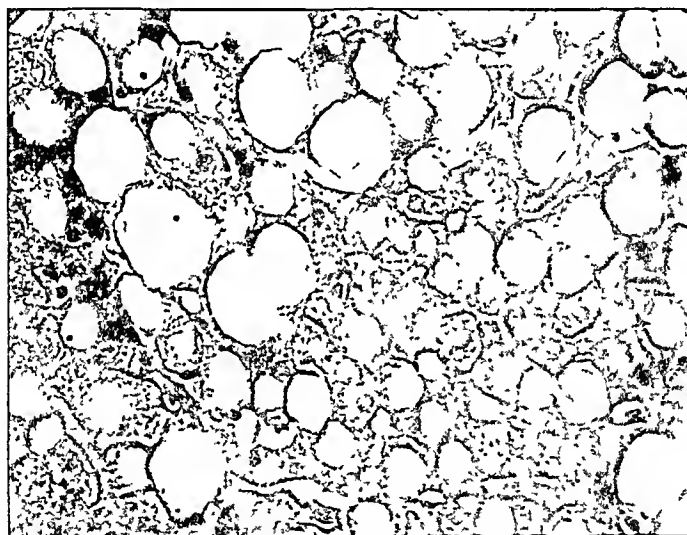


Fig. 1B

Fig. 1. Photomicrographs of the liver before treatment, showing marked fatty infiltration and degeneration (fatty metamorphosis). Hematoxylin and eosin stain. A.—X 140. B.—X 300.

swollen, their cytoplasm, faintly eosinophilic, coarsely granular and occasionally vacuolated, and the nuclei, pale, vesicular and centrally placed. The sinusoids are obliterated by the markedly swollen liver cells. In the periportal areas, there are focal accumulations of lymphocytes with occasional polymorphonuclear leucocytes. The central veins are normal. Diagnosis: Marked fatty metamorphosis of the liver.

Post-operatively, the diabetes became worse, the daily sugar excretion increasing to a maximum of 22.8 Gm. on the third day, accompanied by acetoneuria, 1 to 2 plus; and gradually decreasing to normal on May 21. On May 23, convalescence was complicated by a carbuncle of the sacral region, which required prolonged postoperative care. The dietary management consisted of C 150 P 70 F 70 on May 15 to 17; an 800 caloric soft medical diet from May 18 to July 4, and C 100 P 75 F 60 from July 4 to 8. The total insulin requirement was 350 units, administered between May 17 and June 26. She was discharged from the

hospital on July 8, at which time the hepatic findings were unaltered. Her weight was 165 pounds (75 Kg.).

She returned to the Mandel Clinic on July 23 and periodically thereafter. Although a diet of C 100 P 75 F 100 was prescribed, she rarely ate this amount. On August 12, a glucose tolerance test (50 cc. of 50 per cent glucose intravenously) resulted in the following blood sugar values: fasting, 89 mg.; after $\frac{1}{2}$ hour, 151 mg.; $1\frac{1}{2}$ hours, 181 mg.; $2\frac{1}{2}$ hours, 131 mg.; 3 hours, 130 mg. (abnormal). On September 27, the bromsulphalein test again disclosed 20 per cent retention of the dye at the end of 30 minutes. The liver had remained 10 cm. below the costal margin in the mid-clavicular line on inspiration, was moderately tender on pressure and of increased consistency. The urine had been sugar-free since May 21.

Through the generosity of Dr. Lester R. Dragstedt, a supply of "lipocaine" was obtained, and on September 23, a daily dose of 76 grains (5 Gm.) orally was prescribed for the patient. She was observed subsequently at weekly

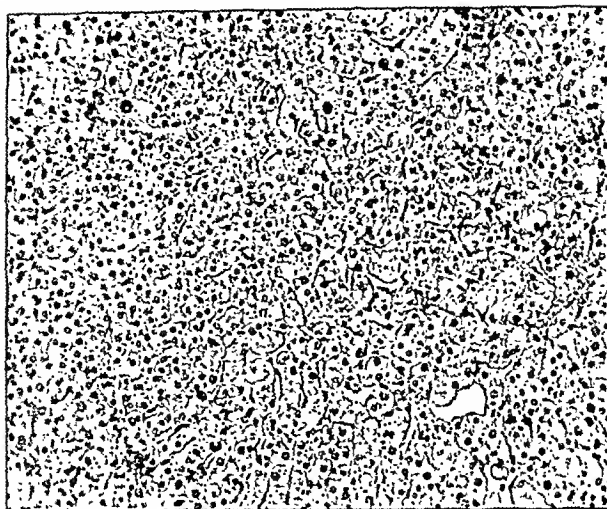


Fig. 2A

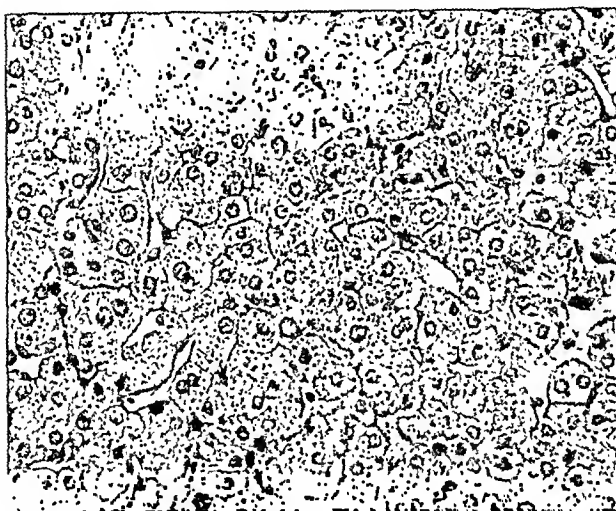


Fig. 2B

Fig. 2. Photomicrographs of the liver after 88 days of lipocaic therapy, showing only slight fatty metamorphosis of the liver. Hematoxylin and eosin stain. A.—X 130. B.—X 300.

intervals. During the first week she seemed "groggy" and tired, and frequently felt "flushed"; these symptoms gradually disappeared. During the examination at the end of the second week, the patient remarked that the liver was "not tender" on pressure. After four weeks of therapy she felt "lots better," i.e. stronger. Although the size and consistency of the liver had shown no change, tenderness could not be elicited on firm, deep pressure. Weight 169½ pounds (77 Kg.). At the end of six weeks, the liver was still of the same size but the edge seemed thinner and less resistant. During the seventh week, there was a marked diarrhoea with 12—15 loose stools daily, lasting for six days. At this time, the edge of the liver was 6 cm. below the costal margin in the mid-clavicular line on inspiration; the consistency was distinctly decreased and the edge definitely thinner. In the subsequent week, the patient regained 2 pounds in weight. The physical findings noted at the preceding examination were confirmed. Nine weeks after therapy was begun, the bromsulphalein test was

repeated, revealing less than 10 per cent retention at the end of 30 minutes. On the following day, December 1, the hippuric acid test showed 108 per cent excretion (3.23 Gm. in terms of benzoic acid) (normal). After ten weeks of therapy the patient felt "fine" and had no complaints. The liver edge was 4 cm. below the costal margin on inspiration, non-tender and of normal consistency. At the next visit (eleventh week), she gave a history of severe sticking pain in the right hypochondrium of 3 days' duration. The liver edge was 1.5 cm. below the costal margin in the mid-clavicular line on inspiration. During the twelfth week, she had another severe biliary colic lasting for one day. Examination revealed no new findings except for a palpable globular mass in the right hypochondrium, extending below the edge of the liver. A diagnosis of cholelithiasis with probable hydrops of the gall bladder was made and surgical intervention advised. Throughout this period of observation, the fasting blood

sugar values ranged from 89—105 mg., and the urine was consistently sugar-free.

She was readmitted to the Michael Reese Hospital on December 21, 1937. Her temperature was 98.6 F, pulse 68 and respirations 18 per minute. Weight 171½ pounds (78 Kg.) The slight pretibial pitting edema, which was again noted, was probably due to a peripheral circulatory disorder. The blood pressure was 156 systolic and 88 diastolic. The urinalysis was negative. Blood examination: erythrocytes, 4.75 million; hemoglobin, 70 per cent; leucocytes, 11900. Sugar, 88 mg.; non-protein nitrogen, 38 mg.; total cholesterol, 348 mg.; cholesterol esters, 154 mg.; icterus index, 10; Van den Bergh, direct, delayed positive; indirect, immediate positive.

On December 24, she was operated upon by Dr. R. B. Bettman. A hydrops of the gall bladder, with a gall stone impacted in the cystic duct and two others lying in the fundus, was found and removed. The liver was remarkably different from its earlier appearance. Whereas it had been yellowish and mottled previously, it was now uniformly reddish brown in color, and normal in size and consistency. A specimen of the liver was again obtained for biopsy and preserved in formalin.

Histologic examination (Figs. 2A and B) reveals a strikingly different picture. The architecture is clearly recognizable now. The liver cords are still swollen. The cytoplasm of the cells is coarsely granular and stains more deeply. Only occasional liver cells are filled with large round vacuoles. The nuclei are pale, vesicular, round or oval and, for the most part, centrally placed, an occasional cell exhibiting an eccentric nucleus. The sinusoids are compressed by the swollen liver cords. In the periportal areas, occasional accumulations of lymphocytes and polymorphonuclear leucocytes are seen; the connective tissue is not increased. The central veins are normal. Diagnosis: Slight fatty metamorphosis of the liver.

Her post-operative course was uneventful, and the urine remained normal throughout. December 31, the fasting blood sugar was 110 mg.; total cholesterol, 288 mg. On January 3, 1938, a glucose tolerance test, injecting 50 cc. of 50 per cent glucose intravenously, revealed the following blood sugar values: fasting, 87 mg.; after ½ hour, 182 mg.; 1½ hours, 108 mg.; 2½ hours, 83 mg.; 3 hours, 59 mg. In the light of Soskin and Mirsky's work (16), this normal tolerance curve may be interpreted as indicating recovery in hepatic function. She was discharged in good condition on January 4, 1938, twelve days after operation. Lipocaic therapy, discontinued during the post-operative period, was resumed on this day.

On February 2, the total blood cholesterol was 354 mg. per cent; cholesterol esters, 156 mg. per cent. She has been observed at bi-weekly intervals and has remained in good condition.

COMMENT

The remarkable recovery in the functional capacity (Chart 1) and in the gross and histologic appearance of the liver, as observed in this instance of fatty metamorphosis following treatment with lipocaic, is of considerable clinical interest. In critically establishing the therapeutic effect of any medication, however, it is requisite that the rôle of the natural course of the disease as well as the incidental effect of all contemporaneous factors be excluded. To fulfill these requirements, our patient was carefully observed for 138 days before instituting lipocaic therapy, and during this period no medication was prescribed. Further, the diet was maintained at a low carbohydrate level in order to obviate the regenerative effect upon the liver known to follow a high carbohydrate intake. Repetition of the liver function and glucose tolerance tests in conjunction with the physical findings indicated a static condition in the liver prior

to treatment with lipocaic. It is clearly evident that the insulin given during the post-operative course, if in any way influential, would have manifested its beneficial effects during the control period. Similarly, the early weight loss can be of no significance, for her weight at the time of the respective biopsies was practically the same.

The photomicrographs of the liver before treatment (Figs. 1A and B) are in all respects identical to those of depancreatized dogs (2, 6, 10, 17), and the second specimen (Figs. 2A and B), obtained after 88 days of lipocaic, is histologically indistinguishable from the appearance of the regenerated liver of dogs following raw pancreas, lecithin, choline or lipocaic therapy (2, 6, 10, 17). Experimentally, more than 16 weeks of pancreatic feeding are necessary to effect a return to the normal fat content (18). Hence, had our second biopsy been made after a longer period of treatment, it seems likely that further histologic improvement would have been manifest.

Another interesting phenomenon not necessarily related to the fat mobilizing principle of lipocaic is the development of hypercholesterolemia following treatment. Although this finding is not in agreement with that of Grayzel and Radwin (12a) in juvenile diabetes, nevertheless, it parallels the observations of Chaikoff and Kaplan (19) on depancreatized dogs receiving raw pancreas. Moreover, the rapid fall in the cholesterol level, noted in dogs when pancreatic feedings were discontinued, was likewise observed in our patient during the post-operative course when lipocaic was withheld, the previous level becoming reestablished after lipocaic was resumed (Chart 1). It has been found (18) that the substance in raw pancreas effective in elevating the blood cholesterol is thermolabile, thus being different from the essential factor in lipocaic and from choline, both of which are thermostable.

The appearance of increased amounts of sugar in the urine, usually observed in dogs during recovery, did not occur in this patient. This finding, however, has also been reported missing in some dogs (5a and 5d). It must be remembered that the increased hyperglycemia and glycosuria following treatment does not represent a primary exacerbation of these symptoms, but merely a return to the state of affairs which existed before the fatty metamorphosis of the liver occurred. Hence the occasional failure of these effects of choline or lipocaic to appear, as in our case, may be due to either of two circumstances: It has been shown that an irritative phase precedes the depression of liver function caused by toxic agents (16). It is therefore possible that our patient had not progressed beyond the irritative phase, and that her carbohydrate tolerance had not yet spontaneously improved prior to lipocaic administration. Under these circumstances, no return to decreased tolerance was to be expected after treatment was begun. This explanation, however, is not in accord with the initially impaired liver function of our patient, as shown by the results of the bromsulphalein, azorubin-S and hippuric acid tests. A more likely explanation of the lack of increased hyperglycemia and glycosuria is based upon the recent observations of Soskin (20), who found that prolonged or repeated fatty metamorphosis of the liver in depancreatized dogs may result in irreversible depression of liver function. In such cases the fat disappears from the liver under the influence of

choline, but gluconeogenesis does not return to its previous vigour. The degree of permanent liver impairment which accompanies the phenomenon may not be detectable by the ordinary liver function tests, but is reflected in the 24-hour blood sugar variation (21).

Finally, whatever may be the mechanism by which the results of lipocaic have been attained, whether by its action as a hormone, or by virtue of its effect upon choline metabolism, or both, its beneficial effects in this patient are clearly defined, and represent the clinical counterpart of the findings observed in experimental animals.

SUMMARY

A proved instance of recovery from fatty metamorphosis of the liver associated with diabetes mellitus following treatment with lipocaic is recorded. Biopsy studies made before and after treatment were correlated with the results of liver function and glucose tolerance tests, cholesterol determinations and with the clinical course. The changes observed represent the clinical counterpart of the findings noted in experimental animals.

Note: The author acknowledges with pleasure the assistance extended to him by Dr. S. Soskin.

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DISCUSSION

DR. ALBERT M. SNELL (Rochester, Minnesota) : I was happy to have the opportunity to hear this interesting report by Doctor Rosenberg. It seemed to me this establishes without much question the value of the administration of lipocaic in fatty metamorphosis of the liver associated with diabetes; perhaps in some of the earlier cases reported by Judd, Kepler and their colleagues, the patients would have been benefited had the use of choline been continued for a longer period, or it is quite probable that lipocaic alone would have been of benefit had it been available at the time.

There is one other condition in which lipocaic is of clinical value; namely, in complete destruction or atrophy of the pancreas. At the clinic we have records of one patient who had proved pancreatic lithiasis; a very large fatty liver; ascites; edema; and who retained bromsulphalein. All of the hepatic changes and other symptoms disappeared under treatment with lipocaic, the diabetes persisting about as before. We have had this man under observation for about two years and a recent report indicates that he is well; his liver is not palpable and he is able to work every day.

Doctor Bollman recently has attempted to determine whether lipocaic is a general protective substance against fatty metamorphosis of the liver. His dogs were given alcohol to the point of intoxication twice a day and a diet high in fat and moderately deficient in carbohydrate and protein. The normal fat ratios were reversed by this procedure. One animal, which received 0.5 gm. of lipocaic per kilogram of diet, had almost a normal quantity of liver fat and the concentration of glycogen in the liver was relatively high. Unfortunately, two subsequent animals which were given large doses of lipocaic and the same diet failed to be similarly protected. Doctor Bollman is continuing these experiments and it may be possible for him to show that lipocaic has some protective effect against fatty metamorphosis of the liver.

DR. EARNEST H. GAITHER (Baltimore, Md.) : Dr. Rosenberg asked me some time ago to discuss this paper.

I am sure we all feel a deep sense of gratitude to Dr. Rosenberg for his excellent and enlightening presentation of this most important subject.

The work is quite new, and we shall anticipate the results of further research; these, I feel, will tend definitely to prove the claims made by those workers who have developed this new theory based upon what at this moment seem quite solid and convincing facts, i.e., those studies by Dragstedt, Prohaska and Harms, who prepared a fat free alcoholic extract of beef pancreas ("lipocaic") which, when fed to depancreatized dogs, proved as effective orally as either raw pancreas, lecithin, or choline, in preventing or curing fatty metamorphosis of the liver; they believe this to be a "fat metabolizing hormone", concerned in the normal transport and utilization of fat.

It was indeed a stroke of good fortune that Dr. Rosenberg had the opportunity of administering lipocaic to a patient with marked fatty metamorphosis of the liver associated with diabetes mellitus, thus correlating the clinical observations with the results of liver function and glucose tolerance tests, and with the gross and histologic appearance of the liver both before and after treatment. Dr. Rosenberg has most convincingly presented the striking results.

This new method of attacking fatty metamorphosis of the liver associated with diabetes mellitus, seems at this time to be an outstanding achievement, and we shall hope that other workers will carry on researches in this

domain in order to provide a large group which will definitely prove the claims and values of this method, which seems to possess true merit.

DR. DAVID H. ROSENBERG (Chicago, Ill.): I have nothing further to add except to thank the discussants for their generous and interesting remarks.

The Effect of Therapeutic Agents on the Volume and the Constituents of Bile*

By

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A REVIEW of the literature reveals many controversial points regarding the factors concerned in bile secretion and bile salt metabolism. Little is known regarding the precursor substances of the bile acid molecule, however, it seems certain that some of the amino acids and vitamins A and D are related to bile acid synthesis (1-7), and that bile acids are formed only by the hepatic epithelium (8-10). Although bile acids and cholesterol or its oxidation products are closely related structurally (11), there is no experimental evidence indicating that the latter are related *in vivo* to bile acid synthesis (12). Protein in the diet increases, while carbohydrate feeding diminishes both volume and bile acid secretion (1, 13-19). The close relationship between bile acid production and urinary nitrogen excretion indicates that bile acid production is intimately related to protein metabolism (21, 22). Fats and soaps are known to influence the flow of bile in the intact animal by their effects on the extrahepatic biliary system, however, the effect of fats on the activity of the hepatic cell is controversial (13, 17, 23-28).

There is considerable difference of opinion regarding the effect of drugs on hepatic secretory activity. This is due in part to the comparison of results obtained by acute experiments on anesthetized animals with those from chronic fistulous dogs, and in part to inadequately controlled experimental procedures with large experimental errors. In order to conserve space, the reported effects on bile flow of some of the more common drugs are tabulated in Table I.

It should be pointed out that in most previous studies on bile secretion conclusions, with few exceptions, have been based on changes in bile volume. It is desirable, at this point, to distinguish between two types of secretory activity, namely, (a) the secretion of water which increases the volume-output of bile without regard for the quantitative amounts of the various constituents, and (b) the secretion or excretion of the individual biliary constituents other than water. Our interests have been directed toward the latter. Before discussing the choleretic (increase in secretory or excretory activity of the liver) properties of the drugs we have studied, it is necessary to consider, briefly, the chemical similarity of the more common bile acids.

THE BILE ACIDS

Only traces of bile acids occur free in bile; essentially all of the bile acids present are paired in peptide-like linkage with the sodium salt of either glycine or taurine. Neither tryptic digestion nor bacterial decomposition in the alimentary tract ruptures this combination (28, 29), thus, bile acids are absorbed from the intestine in their original conjugated form. The glycine and taurine portion of the bile salt molecule is the same in all animals, but the cholic acid part of the molecule differs slightly in some animals. This difference is confined solely to the number and position of the hydroxy groups present.

The determination of the structure of the bile acids has been an arduous task requiring almost a century for its solution, and the awarding of the Nobel prize in 1928 to Wieland and Windaus was a fitting tribute to the brilliant success of these investigators. All of the known bile acids have been submitted to dehydration followed by hydrogenation to be converted into the OH-free parent compound, CHOLANIC acid. Cholic acid is the most common bile acid; its molecule contains three OH groups in positions 3, 7 and 12 (3-7-12 trioxycholanic acid). Desoxycholic acid occurs in the bile of some species in several isomeric forms; its molecule contains two OH groups. The desoxycholic acid of ox-bile and anthropodesoxycholic of human bile are the same substance (3-12 dioxycholanic acid). Isomers of this bile acid have been isolated from goose bile, chenodesoxycholic (3-7 dioxycholanic) acid, and from hog bile, hyodesoxycholic (3-6 dioxycholanic) acid. Lithocholic acid contains one OH group (3-oxycholanic acid); it was first isolated from gall stones and is found in significant amounts only in herbivorous bile.

Another bile acid complex, occurring naturally in bile in traces, but which does not concern the present considerations, is CHOLEIC acid; this is a stable combination of three or more molecules of 3-12 dioxycholanic (desoxycholic) acid in molecular combination with fatty acid.

Aside from the bile acids occurring naturally in bile, there are commercial preparations in which the hydroxy groups have been oxidized to the keto-forms. These constitute the "dehydrocholic" acids; they are probably better known under the trade names "Decholin" and "Ketochole." Such preparations are mixtures of mono-, di-, and tri-ketocholanic acids. "Decholin" is practically pure 3, 7, 12 triketocholanic acid.

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Editors' Note: Substituted for the original article read by same authors at the Meeting of the American Gastro-Enterological Association.

TABLE I
Effect of drugs on bile flow

Drug	Effect on Bile Flow	Observers
Aliphatic compounds:		
Chloral and chloralose	Increased	Chabrol (1930)
Avertin	Doubled	Chabrol (1930)
Ethyl alcohol	No effect	Chabrol (1930)
Ethyl alcohol	Increased with 200 cc. 10%	Okada (1915)
Ethyl alcohol	Decreased	Winogradow (1927), Propkop 1928
Aromatic compounds:		
Salicylic acid	Increased	Doyon and Dufourt (1897), Winogradow (1908), Okada (1915), Specht (1923), Chabrol (1929)
Salicylic acid	No effect	Smyth and Whipple (1924)
Acetyl-salicylate	Increased	Winogradow (1924), Chabrol (1929)
Phenyl-salicylate	Increased	Meissner (1926), Chabrol (1929)
Salicyl-salicylate	Increased	Chabrol (1929), Kaufheil and Rappoport (1932)
Benzoate	Increased	Gumprecht (1895), Klonka (1905), Meissner (1926), Robson (1890), Paton and Balfour (1891)
Phenol, catechol, hydroquinone, Pyrogallol, naphthol, resorcinol, guaiacol, vanillin	Increased	Chabrol (1929) (1931)
Cinephen	Increased	Horsters (1925), Adler (1926), Spurling and Hartman (1926), Meissner (1926), Chabrol (1929), Franke (1930)
Cinephen, purified	Increased	Bradley (1938)
Phenolphthalin	No effect	Tunnicliffe (1902)
Phenolphthalin	Increased	Fleig (1908)
Tetraiodophenolphthalin	No effect	Chabrol (1929)
Calomel	Increased	Pitini and Fernandez (1914)
	Decreased	Doyon and Dufourt (1897), Paton and Balfour (1891)
	No effect	Okada (1915), Stransky (1925), Adler (1926), Smyth and Whipple (1924)
Morphine	Decreased	Picard (1879), Paval et al (1929)

EXPERIMENTAL

The many variables inherent in experimental methods previously available for collection of bile from chronic bile fistula animals is well known to all who are familiar with bile-fistula dogs. For the past two years we have employed an improved method which permits quantitative study of the secretory activity of the liver. The continuous application of a slight negative pressure to the tubing draining the biliary passages has eliminated many of the variables and has furnished quantitative data which reveal that the liver is as constant in its secretory activity as the other externally secreting glands (30, 31). Within the past decade dependable chemical procedures have been developed for the quantitation of biliary constituents. In view of the increasing interest in the chemical composition of bile, it has become desirable to study the effect of certain therapeutic agents on bile secretion, employing these improved physiological and chemical methods (for details see reference 31).

High Fat Diet: Since the lipid fraction of bile is known to aid bile salts in keeping cholesterol in solution, we desired to know if the lipid fraction of bile could be influenced by dietary means. *Purified linseed oil* was selected because it contains considerable unsaturated, diffusible fatty acid which can be absorbed in the absence of bile (33). Two cc. per kilo was fed daily with the regular diet, the latter being reduced sufficiently to cause the daily caloric intake to remain unchanged. (Fat in diet increased from 39 to 60 per cent of the total caloric intake). Over a three day period volume output was increased by an average of 16 per cent, basal bile acid output was unchanged, and cholesterol and biliary lipid output were each increased by an average of 37 per cent.

Commercial bile acid preparations: It is generally agreed that bile salts and their derivatives are the most effective stimulants of bile flow, and experimental or substitutional bile salt therapy in biliary disease is becoming a common clinical practice. As a result, a number of commercial bile salt preparations are available; among the better known of these are Decholin (Riedel-de Haen), Ketochol (Searle) and Bilron (Lilly). Dechacid (Wilson Lab.) is a newer product as yet not on the market. These preparations represent three different types of bile acid derivatives (vide infra).

The comparative effect of the above bile acid derivatives was determined on a number of bile fistula dogs. The data is summarized in Table II (for individual analyses see reference 31). Briefly, the procedure for testing the effects of drugs on biliary constituents was based on the following procedure. During the first three days of a consecutive six day period the animals were maintained on a standard routine without the return of bile. The output of biliary constituents during this period represented control or "basal" output. During the remaining three days the drug to be tested was administered in divided doses following meals. Comparison of the values for this period were made with those of the control period.

Bilron proved to be a potent choleric. This preparation contains the acid-insoluble iron salts of the natural conjugated bile acids of ox-bile. Five grams daily increased volume output by 57 to 116 per cent; cholates were increased by 68 to 234 per cent; cholesterol by 69 to 350 per cent; pigment by as much as 65

per cent, and fatty acids by 59 to 129 per cent. The increased bile acid output resulted from the presence in the bile of cholates administered in this bile acid preparation.

Dechacid contains the *conjugated* bile acids of ox-bile which have been oxidized to the keto- form (conjugated ketocholelanic acids). This preparation was also choleric when administered in daily doses of 3.6 and 5 grams. Volume output was increased by 36 to 79 per cent. Cholate excretion was unchanged (the oxidized derivatives contain no cholates, thus their presence would not be detected by the method used for analysis) but the total bile acid output was increased due to the presence in the bile of the administered keto-cholelanic acids. (Keto-cholelanic acids were determined by a method devised at the Wilson Laboratories, Chicago) Cholesterol output was increased by 30 to 110 per cent while pigment output was not materially altered.

Decholin and *Ketochol* contain the oxidized, unconjugated bile acids of ex-bile (unconjugated ketocholelanic acids), thus, they differ from *Dechacid* only by the fact that they are unconjugated. Five grams daily increased volume output by as much as 190 per cent. Cholesterol output was increased by 10 to 125 per cent with *Ketochol*, and decreased by 28 to 56 per cent with *Decholin*. Fatty acid elimination was increased comparably with all of the bile acid preparations (by 14 to 129 per cent). However, the oxidized, unconjugated preparations depressed bile acid synthesis, as reflected by cholate output, by 12 to 50 per cent. This latter finding has been observed by others (32). Due to the presence in the bile of keto-cholelanic acids, total bile acid output (cholated plus ketocholelanic acids) approximated the cholate output during the control period. Since the *conjugated* ketocholelanic preparation (*Dechacid*) did not suppress cholate synthesis in a similar manner one of two conclusions seems likely. Either the suppressed cholate output occurred as a manifestation of toxicity of "free" ketocholelanic acid on the

hepatic cells, or the synthetic activity of the hepatic epithelium was diverted to the function of conjugating the unconjugated oxidized bile acid molecules.

ASPIRIN, in doses of fifteen or twenty grains daily, increased volume output by 3 to 98 per cent, however, total cholate excretion was reduced by 10 to 35 per cent in four of six dogs. Cholesterol output was not affected consistently, and pigment output was increased insignificantly in three of six dogs. It was found that salicylic acid was present in the bile in concentrations of 12 to 20 milligrams per cent; over eighty per cent appeared in the bile in conjugated form.

SULPHANILAMIDE was tested to determine if dosages comparable to those used clinically would produce toxic manifestations in the liver (decreased bile acid synthesis) and to estimate the concentration of sulphanilamide in bile following its oral administration such dosages. Administered orally in doses of ten and twenty grains (one to two grains per kilo), sulphanilamide produced no significant changes in bile secretion or in the biliary constituents. Likewise, ten grains daily had no influence on the choleric action of ox-bile salts. Analysis of the bile in these experiments showed sulphanilamide to be present in concentrations of four to eleven milligrams per cent, amounts which have been reported to be bacteriostatic for certain organisms.

CALOMEL and **AMMONIUM CHLORIDE** were tested because of the clinical impression that these drugs are of value in promoting bile flow and in inducing clinical improvement in cases of "torpid" livers. Calomel in particular has long enjoyed the reputation of being a stimulant to bile flow. When administered in daily doses of 100 and 200 milligrams, the volume of bile flow was increased in only one of five dogs and decreased insignificantly in three dogs. Cholate excretion and cholesterol output were not altered significantly; pigment output was increased 39, 71, and 74 per cent in three dogs and not materially

TABLE II

Effect of certain drugs on secretion and constituents of bile. 3 day test periods. Values expressed as total output (milligrams) per 24 hours

DRUG	No. Dogs	VOLUME			CHOLATES			PIGMENT			CHOLESTEROL			FATTY ACID		
		C*	T**	% Change	C	T	% Change	C	T	% Change	C	T	% Change	C	T	% Change
Bilron, 5 gms.	4	114	198	+ 74	1420	3212	+126	75	101	+ 39	10	21	+110	671	1262	+ 88
Dechacid, 6 gms.	6	123	185	+ 50	1348	1405	+ 4	127	105	- 17	12	13	+ 50	123	630	+ 49
Ketochol, 6 gms.	8	106	259	+144	1126	1021	- 28	118	160	+ 35	9	16	+ 80	598	1016	+ 70
Decholin, 5 gms.	3	117	146	+ 25	1536	976	- 36	90	75	- 17	11	6	- 45			
Aspirin, gr XV	6	113	180	+ 69	1436	1380	- 4	90	96	+ 7	12	16	+ 33			
Sulphanilamide, gr XV	6	130	135	+ 4	1429	1360	- 5	83	90	+ 8	10	9	- 10			
Calomel, 100 mg.	6	134	136	0	1460	1337	+ 3	86	100	+ 16	12	8	- 33			
Linseed Oil, 20 cc.	2	107	124	+ 16	1192	1312	+ 10	104	132	+ 27	8	11	+ 37	409	560	+ 37

*Control Period.

**Test Period.

altered in two. From this data it seems doubtful that calomel is of any value as a cholagogue.

AMMONIUM CHLORIDE, in doses of 15 grains daily, produced a questionably slight increased flow in three of five dogs and increased cholate output even less definitely. Cholesterol output was decreased by 17 to 54 per cent in all experiments, and pigment was increased insignificantly in three instances.

Since the usual trend of cholate output was less with many drugs studied than that observed with ammonium chloride, we desired to rule out the possibility that the amino groups from this compound might contribute to bile acid synthesis. Furthermore, since urea is known to be a strong diuretic we desired to learn if it might also increase bile flow. When urea was administered orally to three dogs in doses of 5 grams daily, it appeared entirely inert so far as bile secretion was concerned. Thus, any changes in the constituents of bile as a result of ammonium chloride therapy were probably due to the relative acidosis that this drug must have induced in the dosages used.

CALCIUM GLUCONATE was tested because of the relationship of bile to calcium absorption and because this drug is frequently administered in hepatic disease. Given without bile this drug appeared to have no significant effect on bile output or the biliary constituents. Administered with ox-bile salts in doses that are known to elevate serum calcium, calcium gluconate increased the elimination of biliary constituents significantly in only one of four dogs.

Mucin and Chondroitin were tested because these drugs are of reputed clinical benefit in conditions which may be possibly associated with disturbed hepatic function (i. e. peptic ulcer, migraine, and also in Eck fistula dogs). Both drugs were without effect on bile secretion or the biliary constituents in bile fistula dogs.

DISCUSSION

Our data on bile secretion, which has been obtained by a quantitative method in rigidly controlled experiments, indicates that a diet high in unsaturated fatty acids (linseed oil) produces a moderate choleresis and that, except for dog bile, the conjugated bile acids of ox-bile (Bilron and Dechacid) are the most satisfactory agents for inducing choleresis in the dog. Such preparations are true cholericics, i. e. they produce increased flow of bile and increased elimination of biliary constituents. Oxidized, *unconjugated* bile acid hydrocholericics preparations (Ketochol and Decholin) act as hydrocholericics, i. e., they increase chiefly the aqueous fraction of bile. The benzene derivatives, especially salicylic acid, also fall in the latter category.

It seems significant that the oxidized unconjugated bile acid preparations cause an absolute decrease in natural bile acid synthesis. Is this a manifestation of toxic effects on the hepatic epithelium? Certain hepatotoxins, for example small doses of chloroform or phosphorus and some cinchophen preparations, act similarly. It is evident, in the case of the unconjugated ketocholanic preparations, that the suppression of basal bile acid output cannot be attributed to the ketogroups in these oxidized bile acid molecules. If this were the case the conjugated, oxidized preparation (Dechacid) would likewise have decreased natural bile acid output. Ketochol and Decholin differ from the latter only in that they are unconjugated, therefore, the question of conjugation must be pertinent. Though

administered ketocholanic preparations are eliminated in part as such in the bile, the diminished cholate output is not the result of a simple substitution of ketocholanic acid for cholic acid. As much ketocholanic acid appeared in the bile when the conjugated form (Dechacid) was fed as with the unconjugated form (Decholin); yet the basal bile acid output was unchanged with the former and reduced by as much as 50 per cent by the latter. Ketochol, which also depressed cholate synthesis, was accompanied by a considerable increase in ketocholanic acid elimination, which increase augmented the total bile acid elimination to that obtained with conjugated ox-bile salts. Our work indicates that a number of factors must be considered in the selection of a bile salt for therapeutic purposes, e. g., its systemic toxicity when used intravenously, its effect on the liver when given orally for long periods, its effect on the natural composition of bile, its hydrocholeric effect, etc.

Although the benzene derivatives tend to augment bile volume output there seems little indication for the clinical use of such preparations to stimulate bile flow when effective cholericics such as conjugated bile acid preparations are available. The reputed cholagog effect of calomel appears unwarranted from our data, although it does occasionally augment bile volume output slightly. Sulphanilamide, in ordinary doses has no depressing effect on hepatic secretory activity, nor does it interfere with the choleric properties of ox-bile salts. It is eliminated in the bile in concentrations that may make its use in biliary tract infections and in typhoid carriers a rational practice. Studies on this problem are now in progress.

SUMMARY

Using improved physiological and chemical methods, we have investigated the effects on bile secretion of a high fat diet, of bile salt preparations, and of certain drugs used clinically. Three of four commercial bile acid preparations tested increased the output of cholesterol and biliary lipids; linseed oil in the diet likewise increased the output of these constituents as well as the volume of bile.

The *conjugated* bile acid preparations (Bilron and Dechacid) proved superior as stimulants to the flow of bile containing increased amounts of biliary constituents. The oxidized, *unconjugated* preparations (Decholin and Ketochol) increased the aqueous fraction of bile but resulted in an absolute decrease in natural bile acid output.

Salicylic acid increased bile volume output; calomel, ammonium chloride, urea, calcium gluconate, mucin and chondroitin were without significant effect on bile secretion or its constituents.

Sulphanilamide, administered orally in doses of one and two grains per kilo, had no effect on hepatic secretory function and did not interfere with the choleric properties of ox-bile salts. This drug was eliminated in the bile in concentrations that have been reported to be bacteriostatic for certain organisms.

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A Modern Conception of Gastric Secretory Functions

Based Upon Recent Investigations and Newer Interpretations

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WHEN Oliver Wendell Holmes delivered his lecture on "The Contagiousness of Puerperal Fever" he actually presented a theory supported by arguments based upon his own clinical observations as well as upon older material newly interpreted. Though much more scientific in his approach, Semmelweis could not have been more persistent than Holmes in impressing upon others his conviction with regard to the contagiousness of puerperal fever. It must be clear to most of us that contributions to medical knowledge often come piece-meal; all the data may not fit into a harmonious whole but the incomplete story often becomes a probable theory. I hope to make such a contribution.

When the relationship of the stomach and pernicious anemia was discovered, a new field for the study of the gastro-intestinal tract was thrown open. Soon it became evident to some of us that entirely different interpretations could be placed upon older researches and that there existed in the gastro-intestinal tract not only an hematopoietic function but also an intimate motor and sensory overlapping as for example in the poorly understood phases of gastric secretion, which had not yet even begun to be explored.

Without a complete understanding of the normal functions of the gastric mucosa it is hardly possible to interpret pathological changes satisfactorily. So much of the physiology of the gastric mucosa is beyond our ken that successful therapy can hardly be applied when pathologic change takes place. Now we know that there is an hematopoietic function in the cells of the gastric mucosa and we are constrained to ask whether there are also other functions?

GASTRIC ACHYLIA

To begin then we would like to consider the subject of gastric achylia. During the past 5 years we have been led to conclude that gastric achylia is usually relative rather than absolute, false than true, partial than complete, functional than organic. It has been the experience of most of us that with the introduction and utilization of the fractional test meals and hista-

mine many achylia proved to be more apparent than real. Further observations disclosed that the gastric achylia associated with pernicious anemia was a definite persistent achylia. The question arose as to whether the mechanism by which this achylia resulted was different from that associated with certain cases of gastric malignancy or gastritis. Studies of this type at first led to the conclusion that the difference was one of degree, not of kind, but it was difficult to explain why pernicious anemia so rarely followed in long-standing cases of gastritis, even to the degree of atrophy, or was so infrequently associated with gastric malignancy. It appeared that either pernicious anemia was a more general disease than could be accounted for by a gastric locus alone or that it came about only as the result of a combination of gastric changes which occurred very infrequently in instances of gastric achylia due to causes other than pernicious anemia.

INTRODUCTION TO NEUTRAL RED STUDIES

In our clinic we have been able to observe and compare the reaction to numerous test meals with and without histamine. We had adopted the usual criterion for true gastric achylia, that is, failure of response to histamine. In the past 5 years we have become interested in the ability of the gastric mucosa to excrete neutral red. These studies were at first confined to animals and later included humans. However, before analyzing the results it seems essential to remark how few observers realized the inherent possibilities of neutral red as a method of testing the viability of gastric mucosal cells. The literature is too abundant to summarize in this presentation but it is necessary to recall certain key studies which could be profitably reinterpreted today. For example, a careful review of many of the earlier contributions stress the almost unbelievable fact that neutral red is specifically excreted by the oxyntic cell. There are dissenting observations but the consensus of opinion and the better controlled experiments link together, almost inseparably, neutral red excretion with the oxyntic cell. The importance of this observation is highly significant because it immediately introduces us to a possible method of separating the stomach into various parts for study. In other

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words, neutral red has segregated one cell for us and it has accomplished it far more usefully and exclusively than histamine or acid secretory studies in response to test meals because, as has been and will be pointed out, it is able to detect more minute functional capacities of this cell than these other methods.

We, as well as others (1), have observed that pyloric resection influenced and sometimes inhibited fundus excretion of neutral red. Two possible explanations were offered, one that a disturbance of the magenstrasse caused an interruption of reflex stimuli which existed between the fundus and pylorus or second, that there was a hormonal basis, the hormone having its origin in the pylorus. Klein (2) has called attention to the achlorhydria following partial gastrectomy. This achlorhydria is due not to a loss of acid cells, as they are situated in the body and in the fundus of the stomach, but to a loss of the antrum, through which the chemical stimuli of the food (secretagogues) act. However, a small dose of histamine which acts directly on the glandular cells stimulates a normal secretion of hydrochloric acid. In other words, partial gastrectomy does not destroy the ability of the stomach to produce free acid but only interrupts the natural train of events for the secondary phase of the secretion of hydrochloric acid.

The implication of all this work, in addition to the observations based on reliable investigations that pernicious anemia stomachs do not excrete the dye, is far-reaching. Neutral red becomes not only a test for true achylia but also a method by which degrees of impairment of oxyntic cell function may be determined and perhaps also a method of reinvestigating the existence of a possible pyloric hormone. The mere fact that the neutral red excretory test seems to represent the last stage of mucosal activity before complete cessation of oxyntic glandular functions is sufficient to make it replete with possibilities for studying gastric mucosal functions. The test is definitely independent of psychic influence as was pointed out by Henning and Jurgens (3) in a series of 161 cases. Three of their cases demonstrated no secretion of free acid after histamine but a rapid excretion of neutral red.

NEUTRAL RED OUR HYPOTHESIS

A careful consideration of neutral red studies added to our own investigations made it rather clear that neutral red will detect more minutely than perhaps any other test including histamine whether the gastric mucous membrane has latent secretory and excretory possibilities. Furthermore, and because of its selective elimination, it discloses direct information concerning oxyntic cell activity.

THE CLINICAL DATA

Henning and Bach (4) in an interesting discussion, concluded that clinically only the second phase of gastric secretion is studied; this held true for the alcohol-test breakfast, the caffeine test breakfast, as well as Ewald's test meal. Therefore, it is obvious, they maintained that only a partial examination of gastric function is obtained and that no conclusions regarding the physiologic course of gastric secretion instituted by the psychic phase could be drawn. They introduced a method of studying both psychic and chemical phases of secretion and were able to evaluate the function of the individual parts of the stomach. According to their modern conception of the mechanism of secretion the chemical phase of the secretion is related to the function of the mucosa of the pylorus; a direct influence by chemical stimuli of the glands of the fundus presumably does not take place. The first peak of the physiologic activity curve is no doubt conditioned by the parenchyma of the fundus, stimulated by the vagus. This part of the curve tells nothing, therefore, about the functional condition of the glands of the antrum. The second rise of the acidity curve is due to the influence of the secretin on the glands of the fundus. This chemical part of the acidity curve is based, therefore, on the function of both parenchyma segments of the antrum as well as the fundus. From the behavior of these two segments of the acid secretion conclusions may be reached regarding the function of the mucosa of the fundus as well as of the antrum, a possibility which may be considered as a refinement of our diagnostic methods dealing with the gastro-intestinal tract. It could be expected that by the aid of this method isolated functional disturbances of segments of the mucosa could be detected. Psychic inhibitions of the gastric secretion appeared at first during the first phase. This functional disturbance may be designated as functional achylia of the fundus. The isolated achylia of the antrum is characterized by the absence of the second phase and in the presence of a psychic phase in the combined acidity curve. The isolated antrum achylia is observed only in organic diseases.

In a study (30 cases up to the present) which we are now carrying out we have been able to corroborate the greater part of these observations. We have also correlated the excretion of neutral red with these phases. In most instances we found a direct relationship between degree of acid secretion and rapidity of appearance of neutral red. This was especially marked in normal stomachs and in secondary gastric disorders. In all cases of pernicious anemia examined neither a psychic nor an organic phase could be demonstrated

Malignant Neutropenia						Ewald Test Meal	Chemical Phase					
Fasting	Patient A. A.	10 Min.	20 Min.	30 Min.	WBC 1,620		Segm. 38	Lym. 61	Meno. 1			
					30 Min.				45 Min.	60 Min.	75 Min.	90 Min.
Free	0	Neutral	0	0	0	0	0	0	0	0	0	
Total	4	Red 3 cc. Intramus.	4	6	6	4	4	5	5	6	4	
Psychic Stimulation												

nor did neutral red appear. In a case of malignant neutropenia there was an achylia during the psychic phase as well as during the 2nd phase. However, neutral red did appear in the 2nd phase in the 90 and 115 minute specimens. We believe this signifies an incomplete atrophy or lack of function of gastric mucosa which probably would return to function if the primary disease could be improved.

Interestingly enough, some of the asymptomatic gastric achylas were found to excrete neutral red and we were stimulated to inquire whether the excretion of neutral red could be interpreted in terms of sufficient gastric function to prevent symptoms. Our data are not sufficient at present to allow us to form any definite conclusions. We have also had cases of apparent achylia gastrica (0-10) in which neutral red was excreted. Later these cases were found to have free acid and a high total acidity. We believe the excretion of neutral red indicated a possible return of function. All of us have had the experience of ulcer symptoms in the presence of an achylia and actual ulcers have been reported. Though the observation is debatable it has been our experience that these patients are aided by alkalies and are sensitive to acid. It would seem that though apparently achylic they may later be capable of secreting their own acid. We have also had patients who demonstrated no secretion of HCl in the fasting analysis or after an Ewald test-meal but did excrete neutral red. Later a fractional meal showed normal gastric acidity. The symptoms of such patients were usually exaggerated by acid-pepsin medication.

The method of performing the combined gastric function test is very simple but is omitted here to conserve space. We used a 1% solution of neutral red (ph. 5.5) autoclaved at 15 lbs. for 20 minutes. From the point of view of stability we also used a 1% solution of neutral red the pH of which was adjusted to 3.5 by the addition of normal hydrochloric acid. This was also autoclaved at 15 lbs. for 20 minutes. Both were tested bacteriologically before use. We also used the dye prepared freshly in water. However, the studies leading to the preparation of the dye are quite detailed and will be reported in another communication.

From these clinical observations, it seems to us that neutral red will aid in diagnosing both functional and organic achylas of the fundus since its excretion depends only on the integrity of the oxyntic cells.

EXPERIMENTAL DATA

The elimination of dye stuffs by the gastric mucosa in various pathological conditions of the stomach and the study of this elimination experimentally in animals have received rather extensive recognition. However, the clinical application of this data and especially that of neutral red, has been rather sporadic and incomplete. In order to furnish a working basis for our investigations it seemed essential to repeat the study of dye elimination through the gastric mucosa (5). At present we are concerned with neutral red which we have been able to demonstrate in the oxyntic cell by a method (6) heretofore not used as far as we have been able to learn. This is an important contribution since the difficulty connected with the study of vital dyes is that they cannot easily be fixed in situ. It would require too much time and space to review the many procedures which we carried out before we were

finally able to develop a successful fixation method and needless to say, we were at times skeptical of our supposition that neutral red which apparently finds many tissues of the body permeable could manifest selective elimination through the gastric mucosa. There can be no question, however, regarding the conclusion we have reached that the parietal cells are the cells chiefly concerned in the elimination of neutral red by the gastric mucosa. Moreover, Kobayashi (7) was able to show that when the parietal cells secrete HCl in a high concentration, they secrete dyestuffs in a relatively large quantity; there was a parallelism between the two which was not true of pepsin. Henning, (8) too, by direct microscopic study concluded that dyestuff excretion is a function of the fundus glands, and that the antrum glands do not participate in this function. There are, of course, dissenting views but in our work (6) we were actually able to fix the neutral red in the parietal cells, something which had not been hitherto accomplished. The stain was definitely confined to the oxyntic or parietal or acid-secreting cells.

Following a routine study of smaller laboratory animals, we decided upon the white rat as an unusually favorable animal for this work, (6), since the observation was made that the fundus was definitely demarcated after the injection of neutral red. The stomach, too, was small enough for fixation in its entirety.

Since the stomach is normally acid in reaction, it was decided to bring an aqueous or saline solution of neutral red in contact with hydrochloric acid and then to add various other agents. When a precipitate formed, that combination was considered a possible means of fixing neutral red in the gastric wall for most of the agents were really fixing agents. Every procedure singly and in combination used in carrying a section through to its resting place on a slide was tried without success until we chanced upon the report of Pfuhr who obtained excellent results with the "Susa" mixture of Heidenhain in retaining trypan blue. We decided to attempt its application to neutral red. Accordingly, the whole stomachs of rats (starved for twenty-four hours) were fixed, after the injection of 1 cc. intravenously of 1% aqueous neutral red, in the "Susa" mixture (corrosive sublimate 4.5 gm., sodium chloride 0.5 gm.; distilled water 80 cc. to which was added immediately before use—trichloroacetic acid 2.0 gm., acetic acid 4 cc. and formol 20 cc.). They were then transferred from the fixative directly to 90 per cent alcohol and during the course of the same day through absolute alcohol. (These steps are mentioned because in previous experiments the neutral red granules were dissolved out by various agents used in the fixing process. Water and the dilute alcohols were especially likely to wash out the dye). The stomachs were then carefully cut through longitudinally and passed into carbon disulphide (not previously used), and then into a mixture of equal parts of carbon disulphide and soft paraffin. After 8 to 12 hours in soft paraffin the halves were embedded in hard paraffin. Complete serial sections were made at 5 to 7 microns, alternate sections being stained with phloxine-methylene blue as a control on localization of the parietal cells. The experimental sections of neutral red were carried through the alcohols, cleared, and mounted in neutral balsam. Examination of these sections showed that it was possible to retain the

neutral red dye, not as a pure red but as yellowish red, which could readily be detected in the canaliculi of the parietal cells. The localization of the neutral red granules corresponds exactly with the anatomic distribution of parietal cells in the phloxine-methylene blue preparations. The same results were obtained in dogs.

Therefore, by the use of the "Susa" mixture of Heidenhain, neutral red granules were found to be selectively eliminated by the parietal cells of the white rat's and dog's stomachs. Since the oxyntic cell secretes hydrochloric acid and excretes neutral red and since both of these functions are absent in true achylia gastrica it becomes clear that these two tests represent the most important method by which a diagnosis of true achylia gastrica may be reached. Moreover, since the cessation of hydrochloric acid occurs long before the failure to excrete neutral red, as we have been able to demonstrate in animals and humans, it would appear that the HCL secretion function of the parietal cell is more sensitive to obnoxious agents than the neutral red excretory function but since many of the achylia excreting neutral red can be shown to be false the conclusion that neutral red excretion is a better test of minimal degrees of parietal cell viability demands expression. Hurst has also directed attention to the observation that the oxyntic are most delicate cells. To this extent, therefore, the condition of achylia gastrica receives further elucidation.

Furthermore, inasmuch as pernicious anemia remains the most outstanding disease of which true achylia gastrica is a part the question arises as to the importance of the oxyntic cell in that disease (9). It is possible that an understanding of the function of this cell may help to make clear some steps in the mechanism of the production of pernicious anemia. At any rate, as long as neutral red is excreted by the parietal cell there is a possibility that the reaction which interfered with cell function may be reversed or reestablished. Several cases of pernicious anemia have been reported in which apparent cure has resulted. One of the more recent was described by Davidson (10). In his case the stomach regained the power of secreting hydrochloric acid and pepsin and, in all probability, intrinsic factor.

Finally not all dyes are excreted through the same channels. It seems probable that we may look forward to the possibility of determining the secretory ability of various portions of the stomach on the basis of their ability to excrete dyes. Kobayashi's observations are suggestive on this point.

ADDITIONAL DATA

In 1934 when Dodds, Noble and Smith (11) found that the posterior lobe of the pituitary contained a substance capable of inducing a severe lesion of the acid-bearing area of the stomach and when later Dodds and Noble (12) discussed the relation of the pituitary gland to anemia and blood formation and reported the development of a definite severe macrocytic anemia in a certain number of rabbits treated in this manner, it seemed possible that the problem of achylia and pernicious anemia might be placed, at least in part, on an endocrine basis. In interpreting their results Dodds and Noble mentioned the possibility that the control of blood destruction by the reticulo-endothelial system may be vested outside the system itself and may reside in the posterior lobe of

the pituitary gland. Finally, from their observations it seemed justifiable to them to consider the possibility of a hormonal connection between the posterior lobe of the pituitary gland, the stomach, and the blood picture.

With these researches in mind we asked Dr. Dodd's cooperation in an investigation of neutral red excretion of the stomach. The experiments, carried out at our suggestion by Dr. W. C. Cutting, showed definitely that in rabbits both dye and acid secretion are decreased by pituitrin administered intravenously. After the administration of histamine (subcutaneously) and neutral red (intramuscularly) a copious secretion of acid and dye result, only to be practically annulled by pituitrin given at the height of secretion of acid and dye. It was demonstrated that acid and dye ran parallel, another proof that the oxyntic cell is concerned with the secretion of acid and excretion of dye, inasmuch as the pituitrin effect is specifically on the oxyntic cell.

It would appear that these pituitary preparations can produce both an achylia and a macrocytic anemia by their specific effects on the oxyntic cells. In other words, interference with secretion of acid and excretion of dye and the production of a macrocytic anemia are all the outcome of destruction of oxyntic cells. It follows that the oxyntic cell may secrete the intrinsic factor. These results cannot be reconciled with the demonstration of Meulengracht, namely, that the pyloric gland region is the anatomical location of the antianemic principle. Both observations, however, can be reconciled on the basis of our conception which credits the pylorus with the possession of a hormone which acts like secretin and thus activates the oxyntic cell to secrete antianemic factor. In rabbits with oxyntic cell destruction produced by pituitrin the pyloric excitant or hormone is present but the oxyntic cells are unable to react to the stimulus. It does seem worthy of consideration that the potent pyloric powder of Meulengracht acts through the oxyntic cell and not directly upon the hematopoietic system.

Recently Cutting, Dodds, Noble and Williams (13) reported that gastric secretion is markedly altered or abolished by any factor which prevents an adequate increase in blood flow to the stomach. They conclude that their investigations (14) indicate that the posterior lobe of the pituitary gland produces a substance which up to the present has not been dissociated chemically from the vasopressive principle, and which is necessary for maintaining the vascular system in such a state that it is capable of a smooth and regular activity, so that the blood flow to secreting glands such as the stomach may be co-ordinated with the secretion, following the application of an adequate stimulus. They believe their findings demonstrate a new relationship between the posterior lobe of the pituitary, the blood flow, and alimentary secretion; and they suggest an entirely new approach to research on disease in which there is a derangement of the alimentary function. Interestingly enough, Cannon has called attention to an achylia resulting from deficient blood supply incident upon stimulation of the sympathetics which in turn caused a contraction of the splanchnics.

CONCLUSION

As the result, therefore, of a careful consideration

of neutral red studies added to our own investigations it seems rather clear that neutral red will detect more minutely than perhaps any other test including histamine whether the gastric mucous membrane has latent secretory and excretory possibilities. Furthermore, and because of its selective elimination, it discloses direct information concerning oxyntic cell activity.

GASTRIC MUCOSA-HEMATOPOIETIC FUNCTIONS

Few investigators actually realized that the gastric mucosa played so important a role in hematopoiesis until the researches of Castle were so convincingly carried through. These "opened a sesame" which led to many fine contributions and hypotheses. However, there were many cases of pernicious anemia which could not be explained for one reason or another on the principles laid down by Castle and others. Many theories were offered. Among them I called attention (15) to the fact that a Meckel's diverticulum occasionally contains the same cell elements which are present in the stomach and arguing by analogy it seemed perfectly logical to suppose that aberrant gastric tissue may be present in other parts of the body. Such heterotopic tissues are already familiar to us not only in Meckel's diverticulum but also in the esophagus, pancreas and intestine. Before this Association at its meeting in May 1936, I did not consider plausible my suggestion that the gastric factor is perhaps also secreted by aberrant gastric tissue as in Meckel's diverticulum. If this is worth consideration we may argue by analogy that the constant presence of gastric achylia is hardly co-incidental in pernicious anemia. Of course it is possible that because gastric achylia is present gastric digestion is unable to elaborate from food the specific antianemic principle present in liver but it is also possible that the failure of the gastric mucosa to elaborate intrinsic factor is the result of the same process which causes gastric achylia. Moreover, the duodenum and possibly other parts of the digestive system also play an important part in pernicious anemia. In this instance a duodenal achylia may interrupt the elaboration of an antianemic substance. However, we have not been able to demonstrate such an achylia so that it is possible that the failure to elaborate the antianemic factor may simply be due to functional or organic dysfunction of the specific cell concerned in its elaboration. It would seem as Braun (16) concluded, that the hormone which is active in pernicious anemia is produced by both the gastric and duodenal mucous membrane of normal persons. The work of Meulengracht would also lead to the same belief except that his demonstration of the antianemic potency of pyloric gland substance seems hardly capable of explaining many cases of pernicious anemia. Meulengracht and Schiodt (17) found considerable pepsin and rennin activity in the preparations from the fundus and little in those from the cardiac and pyloric portion of the stomach of swine. They concluded that pepsin and rennin are probably secreted by the fundus glands only and they established physiologic and anatomic dissociation between pepsin and the antianemic factor in the stomach. Greenspon's work (18) although not substantiated in its major claims, demonstrated the antagonism of pepsin toward the antianemic factor. But pepsin is secreted for the most part from the oxyntic cells of the stomach and

estimates are given of from 25 to 80 times the secretion of pepsin by fundus cells as compared to pyloric cells. In fact some observers doubt any actual secretion of pepsin from pyloric cells.

Now we come to a major theory which I hesitate to present. It runs thusly. We have independently been able to demonstrate that neutral red is eliminated selectively by the oxyntic cell of the stomach. It has also been shown that its quantitative excretion not infrequently runs parallel to hydrochloric acid secretion and that it is influenced by the pylorus. Since pepsin tends to inactivate or antagonize antianemic factor it would seem to be poor bodily economy to have it secreted by peptic cells; moreover, since failure to secrete hydrochloric acid and excrete neutral red, both concerned with oxyntic cell viability, determine the existence of true achylia and since without true achylia true pernicious anemia can hardly be presumed to exist, is it not logical to inquire into the possible role which the oxyntic cell plays in pernicious anemia? Even though complete gastrectomy may not be followed consistently by pernicious anemia *it has occurred*. Of more importance are three other factors: (1) the difficulty of excluding all oxyntic cell tissue as is shown by the recurrence of acid secretion after gastrectomies of various degrees, (2) the plausibility of the existence of aberrant gastric tissue and thirdly, the time factor, namely, how long does it take to develop pernicious anemia? The latter undoubtedly depends upon the diet and vicarious intestinal digestion as well as the amount of antipernicious anemia factor already stored up.

In other words, we must investigate the gastric mucosal functions from the point of view of specific cell activity. To this end, we set out to perform a group of experiments based on the possible presence of a pyloroduodenal hormone and another group which would test the likelihood of the pepsin-inactivating theory on the antianemic factor. We had in mind two possible hypotheses. The first supposed that if a pyloro-duodenal hormone existed then the effect of pyloric-gland substance as reported by Meulengracht could hardly be directly potent but must act upon some other substance to produce secretion of antianemic factor much as secretin acts. The second supposed that if depepsinized fundus could be shown to have antianemic properties then the oxyntic cell must be reconsidered as a potent source of intrinsic factor.

HORMONE. OUR HYPOTHESIS

Experiments (19) with various pyloric extracts suggest that a pyloric secretion may exist and the conception is offered that a composite pyloroduodenal hormone may participate in the elaboration of intrinsic factor as well as hydrochloric acid. The belief is also expressed that the hormone may contain histamine as one of its constituents but does not depend upon histamine alone for its several functions. An hypothesis worthy of further investigation would credit the pyloroduodenal mucosa with the elaboration of a hormone which stimulates the secretion of an intrinsic factor by the gastric glands which, in turn, acts on food materials to produce substances that prevent pernicious anemia.

THE CLINICAL DATA

As a result of our previous studies the idea suggested itself to us that the pylorus (and duodenum)

may be the possessor of a hormone which forms the activating or releasing stimulus for secretion of the "intrinsic factor of Castle." In the past others have called attention to a pyloric (duodenal?) hormone, gastrin by name, which was thought by some investigators, to be fundamentally important in producing one phase of the gastric secretory cycle. Since these studies appeared before Castle's contributions to the elucidation of the mechanism of pernicious anemia, the proof of the degree of potency of pyloric extracts was judged primarily by the amount of acid their administration stimulated. Even with so definite an indicator the conclusions reached by different groups of investigators were in conflict. It has recently been suggested by us (19) that the gastric hormone (pylorus, duodenum) may be associated with the intrinsic factor. As a preliminary approach to the problem we decided to make pyloric extracts using acid secretion as a numerical measure of their potencies and hoping to correlate acid secretion with intrinsic factor secretion, for it was our conception that a composite pyloro-duodenal hormone which stimulated acid secretion may possibly stimulate antianemic, intrinsic factor, secretion. These increased secretions could be therapeutically tested in swine with macrocytic anemia produced by the method of Rhoads. This is an excellent and tremendous field of research which figuratively begs all of you to enter it.

Many workers are of the opinion that the pyloric hormone is identical with histamine but in reviewing the evidence in favor of and against the existence of a pyloric hormone one is left rather in doubt, not only as to its identity with histamine but also as to its existence. There is no question but that Meulengracht's recent contribution (20) seems to have demonstrated that the pyloric gland region has antianemic potency but it is important to recall the older researches of Lim (21). Lim believed it probable that by adopting different methods of extraction the order of potency of pyloric, cardiac, duodenal, fundic, jejunal and ileal extracts could be so altered as to obtain results similar to those of Popielski who found fundus extracts to be as active as those of the pylorus in stimulating digestive secretions. Consideration of this belief in the light of Greenspon's work as well as in the light of some of our own researches now in progress, suggest a whole new field of gastric physiology. Moreover, on the basis of anatomical structure alone the fact that fundus and pylorus extracts may have equal potency must at least suggest that their mechanisms of activity differ.

Ivy (22) has reported that an acid extract of the pyloric mucosa, when injected hypodermically, stimulates gastric secretion. Crystalline histamine has been isolated from such an extract and Ivy believes that the evidence indicates that it is the sole secretory excitant of such extracts; that is, gastrin and histamine appear to be identical. However, it seems clear to most of us that histamine is not known to be a stimulator of intrinsic factor secretion and it would seem plausible to consider that a gastric hormone which has this property must be something other than histamine or something in combination with histamine.

There is another interpretation of Meulengracht's work which possibly offers a more consistent explanation of the various results obtained, especially in the light of our neutral red experiments. It is possible, for example, that the effect obtained after feeding

pylorus powder is due to the activation of oxyntic cell to secrete its contents which may perhaps include intrinsic factor rather than to the supposed presence of intrinsic factor in the pylorus powder. The absence of excretion of neutral red in pernicious anemia stomachs demonstrates in my opinion, not only a failure of fundus secretory activity but also a failure of the normal activating stimulus supplied by the pylorus. In other words, this is a mechanism which we know already exists in the human organism as demonstrated in the mode of action of pancreatic secretin. If the fundus plays only a secondary role in pernicious anemia it would be difficult to explain the remarkable consistency of achylia as well as the occasional changes observed in the microscopic studies of oxyntic cells. On the other hand, if duodenal, pyloric and cardiac powders are in reality activating substances for fundus gland secretion an explanation is possible of certain cases in which acid secretion and intrinsic factor secretion have been known to return. This explanation includes the probable fact that neither pyloric gland region nor fundic gland region were entirely atrophied. In other words, both were ready to function when properly treated. It seems possible, therefore, that pernicious anemia is not an incurable disease, that it is, moreover, curable if the treatment changes from substitution therapy to a type of therapy the purpose of which is to stimulate pyloric gland activity of the affected individual. Such therapy may include the administration of pyloric gland powder temporarily not only as substitution therapy but also as stimulative to the pyloric gland region which in the meantime must be relieved of any local lesion which interferes with its activity. The outlook is more optimistic than in diabetes because oral treatment is effective and the pyloric gland region is so widespread probably including many aberrant rests which make it altogether likely that proper stimulation will bring enough of them into activity to result in the cure of the disease. It is also not impossible to conceive that the pyloric (including duodenal) hormone or even histamine or some similar preparation is the key to the cure of pernicious anemia. If Meulengracht's work is to be interpreted as it is in his article, then in cases of pernicious anemia the pylorus and duodenum may be expected to show some organic or perhaps some detectable functional impairment of secretion. However, reports of histological studies of the stomachs in cases of pernicious anemia, if reporting any change at all in the stomach, usually stress oxyntic cell changes.

That the appearance of pernicious anemia may not be an irreversible reaction is suggested by a number of observations. Castle (23) has pointed out that the deficiency of the gastric factor is apparently the dominant mechanism in Addisonian pernicious anemia in relapse. He believes it probable, however, that the gastric defect is relative rather than absolute. Goldhamer (24) has demonstrated that the intrinsic factor of Castle is present in pernicious anemia stomachs but in decreased amounts while Castle and Minot (25) suggest that the existence of residual amounts of intrinsic factor probably explains the "spontaneous" remissions sometimes formerly observed, especially under optimal nutritional conditions with high-protein feeding. Castle, Heath and Strauss (26) have demonstrated the recrudescence of gastric factor in one patient after treatment with liver extract. Such was

also apparently the case in the patients observed by Barnett (27). This observation probably explains the response of occasional patients with pernicious anemia to the oral administration of extrinsic factor, especially of autolyzed yeast in large amounts. Castle (23) also calls attention to the demonstration of the recrudescence of intrinsic factor in a patient with pernicious anemia who originally secreted free hydrochloric acid without intrinsic factor in the gastric juice. Strauss and Castle (28) point out that at least in some instances of pernicious anemia of pregnancy the administration of extrinsic factor before delivery may produce no effect upon blood formation. After delivery, however, this material may induce clinical improvement and a reticulocyte response which may then be augmented when normal juice is added. The disappearance of the intrinsic factor of the gastric juice during pregnancy is occasionally paralleled by the disappearance of the hydrochloric acid, which likewise may return after the birth of the child.

Suggestive also is the report of Schiff and Tahl (29) that the oral administration of single doses of desiccated hog's stomach stimulates the secretion of free hydrochloric acid in normal persons and in patients with hypochlorhydria and apparent achlorhydria. The prolonged administration of desiccated hog's stomach in cases of genuine achlorhydria or achylia gastrica may cause the disappearance of symptoms without the return of free hydrochloric acid.

EXPERIMENTAL, DATA

In our work (19) pig's pyloric extract was used on dogs but inasmuch as there are conflicting opinions regarding the presence of the anti-anemic factor in the stomach of a dog the interpretation of some of our findings must be made with care. Nevertheless, Morris and his coworkers (30) have found dog's secretion potent insofar as hematopoietic activity is concerned.

The methods of preparation of our extracts from the pylorus mucosa of the hog's stomach have already been published (19). The extracts were divided into 4 portions as follows: supernatant and precipitated sodium hydroxide portions and supernatant and precipitated hydrochloric acid portions. The original combined alkaline portions were tested pharmacologically and no depressor substances were found whereas the acid portions contained the equivalent of .0004 mg. histamine per 1 cc. Later determinations of other preparations disclosed that NaOH and HCl supernatant contained histamine-like substances whereas NaOH precipitated portion did not contain any depressor substances. Our HCl precipitated portion was not satisfactory; the observations were few and inconclusive. Histamine controls were used throughout these observations. NaOH (S) was found to stimulate gastric acidity. It may be supposed that this is due to its histamine content but on the other hand, the HCl (S) as prepared by us, was impotent. The activity of NaOH (S) developed on standing 10 days. No potency was present before that time even when administration was performed intraperitoneally and intravenously. A trypsin odor developed after 10 days but trypsin controls ruled out any part which it may play.

These experiments have as their object the discovery of a possible active principle in pyloric extracts prepared by the method described. Since gastric acid titrations give quantitative readings, that index was used to detect any potency of the extracts. Thus far,

there is sufficient evidence to stimulate further investigation of the supernatant alkaline extract. This portion of the extract was found to contain histamine-like substances but its activity appeared after a period of delay during which there developed a trypsin odor. This odor was found not to be due to trypsin activity and it could not be due to peptic activity since it developed when the pH was 7.8. It is possible that sufficient enzyme was present to break down a protein and release a hormone and it seems to us that this period of delay allows for the liberation of precisely such an active hormone which may contain histamine but is rather a composite hormone capable of stimulating not only acid and pepsin but possibly also intrinsic factor. Fouts, Helmer and Zervas (31) believed that during their procedure of concentration by vacuum distillation, a hormone was released or activated.

This data does not refute the assumption that there may possibly be a pyloric hormone which operates as does pancreatic secretin. Pyloric gland therapy may simply be replacement therapy but it may, after its absorption, also stimulate oxyntic cells to secrete intrinsic factor. Furthermore, it is worth considering whether the oxyntic cell is capable of two types of secretion, one an acid secretion which is external in nature, the other an intrinsic factor which may be primarily an internal secretion although it obviously also appears in the gastric juice.

The author realizes that this part of the work is inconclusive at its present stage of development but it at least suggests an approach to the demonstration of a pyloro-duodenal hormone. All previous researches on gastric hormones should be repeated and re-interpreted on the basis of the newly discovered hematopoietic functions of the gastro-duodenal region. We suggest that a pyloroduodenal hormone could have the same "double play" characteristics of the pancreatic hormone, secretin, which is formed by the epithelial cells of the duodenum under the stimulus of acid contents from the stomach, and only then is available to excite pancreatic secretions. Similarly, who knows but that the pyloroduodenal hormone may stimulate the oxyntic cells to secrete the intrinsic factor (also, but perhaps incorrectly, called addisin). We do not believe a pyloroduodenal hormone could be the intrinsic factor for in that case too, many inexplicable problems would arise, but if it were the "sine qua non" necessary for the production of intrinsic factor by the oxyntic cells then a possible logical theory presents itself. If we could conclusively and consistently demonstrate a potent pyloric extract it would remain (1) to determine how closely this is related to histamine, (2) to correlate the gastric secretion it produces with intrinsic factor secretion, and (3) if results warranted it to determine the therapeutic effect of the pyloroduodenal hormone in increasing intrinsic factor secretion in swine with a pernicious anemia syndrome produced by dietary deficiency.

ADDITIONAL DATA

Granting, as all of us will, that pepsin only partly inactivates intrinsic factor it immediately is apparent that the gastric function would be very uneconomical if intrinsic factor were produced in peptic cells. It would seem that either intrinsic factor is produced in an independent cell or in the mucous or oxyntic cells. Careful studies in animals and man have not as yet disclosed any cells or group of granules, the special

function of which it is to secrete antianemic principle. I have made such studies under supervision and I have carefully reviewed (15, 32) the histological work of others as well as special staining methods without being able to shed any light on the exact locus of intrinsic factor formation. Surely the cells of the pyloric gland region have no distinguishing granular characteristics. On the other hand, there are many correlations between intrinsic factor and acid secretions to stimulate the imagination and to suggest investigations. These are the inactivating property of pepsin which is a secretion primarily of the fundus glands, the practically constant association of achylia gastrica and pernicious anemia, the report of a possible association between polycythemia and duodenal ulcer, the absence of ulcer in pernicious anemia and the demonstration that destruction of oxyntic cell tissue by pituitary extracts, as noted by Dodds and his group, with the production of achylia and a macrocytic blood picture in rabbits, at least suggest that the oxyntic cell reacts in direct proportion to the amount of antianemic factor secretion and it is not a far cry to suspect that this same cell may have 2 functions, one an external secretion of hydrochloric acid, the other secretion, primarily internal, of antianemic principle.

The unusual characteristics of the oxyntic cells have been observed by authoritative investigators of the histology of the cells of the gastric glands. For example, it is pointed out that each possesses a remarkable system of secretory canaliculi which discharges into the lumen of the gland. Might this possibly suggest internal secretion? Structural differences corresponding to physiological changes are not easily made out. The parietal cells seem not to undergo any morphological changes in connection with the various stages of functional activity.

Evidence suggestive of linking the manufacture of gastrin with the "mucoid" cells of the glands of Brunner, as well as with the pyloric glands of the stomach has been advanced by Murray (33). Murray found that when that part of the duodenum which contains Brunner's glands is used the secretion by the stomach is greater, more HCl and pepsin being produced. When parts that do not contain Brunner's glands are used the effect is insignificant in almost every case. Murray excluded the effect of histamine in these experiments for histamine given intravenously in cats causes practically no response. It must be recalled that Brunner's glands are exactly those to which antianemic potency has been attributed by Meulengracht. Therefore, since the stimulation of acid and pepsin secretions are brought about by a hormonal mechanism, it seems plausible to assume a similar mechanism for intrinsic factor or antianemic principle. Moreover, Aschner and Grossman (34) point out that extracts of the duodenal mucosa containing Brunner's glands injected intravenously cause secretion of pepsin and hydrochloric acid by the stomach, thus resembling antral glands in function. It becomes clear that functionally and histologically the pylorus and duodenum are related.

Furthermore, it is interesting in this connection to recall the studies of Downs and Eddy (35) on the influence of secretin on the number of erythrocytes in the circulating blood of rabbits. They were able to demonstrate a stimulating effect by secretin presumably upon bone marrow. They also observed that the subcutaneous administration of secretin to anemic

animals produced a much more rapid improvement than could be obtained by dietary adjustment alone. These experiments deserve further study.

In his original researches Castle pointed out that the intrinsic factor is not present in the duodenal contents from which gastric juice had been excluded. If duodenal substance has antianemic potency and if duodenal contents do not have such potency then either the antianemic substance is secreted internally or the duodenal cells secrete a secretin-like material which when absorbed stimulates secretion of antianemic principle in the gastric contents.

At this point it should be stressed that the absence of pernicious anemia after gastrectomy is due to the fact that all oxyntic tissue is not removed from the stomach (partial gastrectomy) or even when it is, which is rare, aberrant oxyntic tissue is still stimulated to secrete by the pyloroduodenal hormone. Moreover, complete removal of the pylorus still leaves the duodenum which apparently has similar properties so far as the secretions under discussion are concerned.

CONCLUSION

It becomes evident from the preceding material that the problem of "gastrin" remains a disputed one as we have already indicated. It cannot be denied, however, that the glands of Brunner and the pyloric glands have similar functions with respect to hematopoiesis. The cells of these regions have different functions from those of the fundus according to most authorities. If, therefore, antianemic potency is proved to be present in the fundus glands then it would seem likely that the pyloric gland region with its antianemic potency demands a different explanation of its mechanism of action than the replacement of actual antianemic material. That different mechanism suggests itself; namely, a gastric secretin analogous to pancreatic secretin.

It is for these reasons that we have had the courage to hypothesize the presence of a pyloroduodenal hormone which activates oxyntic cell secretion of intrinsic factor. A disturbance in this mechanism would result in a true macrocytic anemia, that is, one in which the antianemic principle is absent either as a result of loss of the activating pyloroduodenal hormone or as the result of non-functioning oxyntic cells (including aberrant tissues). However, there is another large group of conditions in which a macrocytic anemia may occur; these are dietary deficiencies; in other words, purely the result of an absence of extrinsic factor. The latter group are not true pernicious anemia since the intrinsic factor mechanism is still present but is interfered with by a debility due to dietary lack. Others concur in this explanation. Such macrocytic anemias, if not of too long standing, respond quickly to the administration of the substance responsible for the dietary lack; the true pernicious anemia may be an end-result of extrinsic factor deficiency only because the anti-anemic principle secretion is interfered with by general glandular asthenia.

PEPSIN HYPOTHESIS

Pepsin is secreted mainly if not entirely by the fundus of the stomach. Pepsin may antagonize intrinsic factor potency of the fundus.

PEPSIN. CLINICAL AND EXPERIMENTAL DATA

Histological studies of gastric and duodenal cells

lead to the conclusion that the fundus may possibly elaborate the intrinsic factor but that its impotency in clinical tests may be due entirely to its pepsin content. When physiological investigations are added to these it is interesting to note that the very cells to which are attributed those properties necessary to combat pernicious anemia are also attributed the possession of a hormone capable of stimulating hydrochloric acid and pepsin secretions. If acid and pepsin secretion are brought about, at least in part, by this humoral mechanism, it follows that the antianemic principle or intrinsic factor may also possibly result from a similar mechanism.

As a result of Meulengracht's work there is prepared in Denmark a commercial powder, known as Pylorin, which represents the pyloric-gland region. It has about the same activity as Ventriculin. However, whole stomach (Ventriculin) should be less potent than pyloric-gland stomach unless the fundus has anti-anemic potency; otherwise the lack of potency in the fundus would diminish the potency of the whole stomach preparation. Moreover, if Greenspon's conception of the importance of pepsin is confirmed then it is that substance which inactivates fundus anti-pernicious anemia potency inasmuch as pepsin is so predominant in fundus tissue. Both Ventriculin and Pylorin have proteinaceous muscularis to act as an adsorbent of pepsin according to Greenspon, or as a source of extrinsic factor according to Castle.

We have reported elsewhere (36) our studies on the rôle of pepsin in pernicious anemia. Our materials, consisting of cardiac, fundic, pyloric and whole stomach mucosae were depepsinized according to the method recommended. Interestingly enough, as far back as 1922, Lim (21) had observed that the activity of the extracts which he used in producing gastric secretion depended in a measure on their mode of preparation. The order of potency of extracts of the mucous membrane of the stomach and small intestine he found to be of the following descending order: pyloric, cardiac, duodenal, fundic, jejunal and ileal but he believed he could change the order of potency by adopting different methods of extraction. Perhaps this helps to account for the confusing reports of Henning and Brugsch (37) (1931), Gutzeit and Hermann (38) (1931), Henning and Stieger (39) (1930) and later in 1934, Henning (40), regarding the comparative potency of cardia, fundus, pylorus and duodenum. Finally, however, the impression is gained that the pylorus is more potent than the other portions as regards its effect in combatting pernicious anemia. Meulengracht (20) in 1935 reiterated this conclusion. Nevertheless, the mere fact that fundus mucosa was found to have some potency is important for it suggests that perhaps after all the presence of pepsin may interfere with the activity of fundus tissue. For example, Henning and Stieger (1930) reported that by administering the mucous membrane of the body of the stomach and that of the antrum pyloricum separately they found that both possessed the same blood regenerating power, and by proving that neither the one nor the other possessed a peptic ferment of any account *in vitro*, they believed they had confirmed the assumption that the effect of the powder was independent of peptic digestion of protein and was a primary and direct one on blood regeneration.

To test the hypothesis that pepsin is antagonistic to the antipernicious anemia factor in stomach we

treated 3 patients with pernicious anemia with depepsinized whole stomach mucosa and depepsinized fundus and pylorus mucosa, obtained from the hog's stomach under conditions considered proper for preserving anti-pernicious anemia potency. We were unable to establish any effectiveness in these preparations alone or with the addition of extrinsic factor. One exception was noted in the use of depepsinized pyloric mucosa which manifested a minimal, though definite, antipernicious anemia activity when the extrinsic factor was added. However, we have reason to doubt the possibility of completely depepsinizing fundus tissues by present methods and we suggest that the process of depepsinization may not always result in the same end-product. In one instance an active product may be obtained, in another an inactive one. Further studies support this belief. Consequently, unless disproved, Greenspon's demonstration of the antagonism of pepsin toward the antipernicious anemia factor (Castle's intrinsic factor) considered along with the known adsorptive capacity of protein and coupled with the histological knowledge of peptic cell predominance in the fundus of the stomach, all suggest a rôle for the fundus in pernicious anemia.

In view of the inactivity of our depepsinized products we questioned the status of intestinal permeability. However, the response to products of known potency, though submaximal, was enough to rule out the factor of intestinal impermeability. The possibility seemed apparent that the process of depepsinization could have inactivated the intrinsic factor. There was no doubt as to the adequacy of our sources of extrinsic factor. We proceeded to treat a patient (41) with typical pernicious anemia with simple desiccated stomach mucosa without any attempt being made to remove the pepsin or to go through the various extractions as described by Greenspon. This preparation proved to be completely satisfactory as a source of intrinsic factor and we, therefore, assumed that the process of depepsinization destroyed rather than enhanced the potency of these preparations. It is important to keep clearly in mind that even if the process of depepsinization inactivated the antipernicious anemia potency of these preparations that result does not necessarily mean that the absence of pepsin *per se* decreases the potency. In other words, a distinction must be made between the physico-chemical changes occurring during depepsinization and the theoretic removal of pepsin without subjecting the mucosa to any changes which might influence the antipernicious anemia potency.

We decided to repeat the administration of depepsinized preparations in increased dosage to two other patients in order to be sure that the maximum dosage of 40 grams each day, as already reported, was sufficient. Two patients were fed with 50 grams of depepsinized material each day. This would insure adequate dosage. Both patients were ideal for the experiment not only because their counts were low but also because they represented typical uncomplicated cases (no neurological signs or symptoms) of pernicious anemia. The first patient's blood did not respond to adequate dosage of depepsinized pylorus mucosa administered orally along with the extrinsic factor. On the other hand, oral and intramuscular therapy of known potency produced a characteristic response.

Curiously enough, the depepsinized fundus material

administered in the same manner was followed by a reticulocyte response of 7% on the 6th day after the onset of treatment. Whether this response, in the light of our previous data, was due to depepsinized fundus mucosa or to some extraneous factor or was spontaneous, it is difficult to determine with certainty. The expected maximum reticulocyte percentage, after desiccated stomach given orally, is about 40% for the level of this patient's blood. The response, therefore, is distinctly minimal. Nevertheless, is it not possible that depepsinized fundus material has antipernicious potency and that the reaction of this patient bears out our predictions that the process of depepsinization does not always result in the same end-product, that the overwhelming presence of pepsin in the fundus conceals its hematopoietic function and that the process of depepsinization rather than the absence of pepsin may account for the inactivation of intrinsic factor? This is further supported by the observation that one patient treated with depepsinized pylorus mucosa plus extrinsic factor led us to conclude that pylorus mucosa had hematopoietic potency whereas a second patient treated with the same material prepared at another time did not react. On the other hand, a patient treated with depepsinized fundus mucosa led us to conclude that it was completely inactive whereas another patient reacted to the same material prepared at another time. Further studies are needed to bring these rather confusing results to a definite and perhaps significant reconciliation. If fundus tissue has antipernicious anemia activity then this evidence supports our hypothesis concerning the action of a pyloroduodenal hormone. It is hardly possible that the increased dosage helps us explain our results since both pylorus and fundus were administered in equal doses in both studies.

Further studies of depepsinized stomach mucosa were made with pigeons but we have purposely excluded that data not only because it is controversial but because there is not sufficient time to present it adequately. I hope to do so on another occasion.

CONCLUSION

The influence of pepsin on antipernicious anemia activity of gastric tissue cannot be disregarded. An understanding of its exact rôle will require further study.

THE CONCEPTION SUMMARIZED

Neutral red may be very useful as a specific test of oxyntic cell function. At the same time it seems to detect a more minute degree of oxyntic cell viability than any other test at our disposal.

The study of neutral red excretion also suggests a pyloric control factor in oxyntic cell activity. Studies of pyloric extracts suggest the same conclusion. Since pylorus and duodenum are so intimately interrelated functionally and anatomically the hypothesis is offered that a pyloroduodenal hormone may regulate oxyntic cell activity. But pylorus and duodenum are also important in providing pernicious anemia-preventive factor. The likelihood that this activity of the pyloroduodenal region is entirely separate from the hormonal function appears to be remote. Therefore, the effort is made to demonstrate an interrelationship between all gastric secretions including the intrinsic factor.

Moreover, pepsin is antagonistic to anti-pernicious anemia activity. But pepsin is secreted by the fundus

of the stomach. If depepsinized fundus substance is potent in pernicious anemia then its mechanism of action must be different from depepsinized pylorus substance. Upon this demonstration the hypothesis of a pyloroduodenal hormone may also be substantiated.

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DISCUSSION

DR. BORIS P. BABKIN (Montreal, Canada): I listened with great interest to your paper, Dr. Morrison. I don't think that I can discuss the anti-anemic factor because

the problems in which I am interested are rather far from this field. In some of your results, however, I am very interested. Thus, for instance, you have seen that the volume of the secretion depends greatly upon the activity of the parietal cells. We came to the same conclusion, which was based upon some different experiments. We believe that the whole fluid of the gastric juice is practically supplied by the parietal cells. The peptic, mucoid and mucous cells seem to secrete very little fluid. Again, in the case of a gastritis, you found in the gastric contents pepsin, but the amount of fluid was extremely small. In other words under these circumstances for some reason only the function of the parietal cells was paralyzed.

With regard to the pyloric hormone, I was glad to hear that although you couldn't purify it completely from histamine, it seems you are on the way to get something which is not histamine. As I have previously stated, I could never agree that the pyloric hormone is histamine. Histamine undoubtedly plays a certain part in the regulation of the gastric secretion, namely, in the nervous phase, but probably not in the chemical phase. There is something else which acts as a hormone during the chemical phase. Possibly it is the substance which Dr. Komarov extracted from the pyloric mucosa using trichloroacetic acid.

DR. SAMUEL MORRISON (Baltimore, Maryland., closing the discussion): I have no remarks to add except to thank Dr. Babkin for his discussion.

Editorials

A NEW METHOD FOR DETECTING ULCERATION OF THE DIGESTIVE TRACT

ONE of the most interesting suggestions recently made in the field of gastro-enterology is that of Dr. E. E. Woldman of Cleveland, who got the idea that when a patient has an ulcerated area in the bowel, the normal high degree of impermeability of the mucosa to many substances should be impaired. Reasoning along these lines I have long suspected that when a person who has always been able to eat some food, such as crab, with comfort, suddenly becomes highly allergic to it, it is because the formation of an ulcer has opened up a path through which much of the crab protein has gone unchanged through the liver into the blood. Somewhat against this theory, however, is the fact that during a study of the food-sensitiveness of 500 persons, I gained a strong impression that persons with ulcer and cancer of the stomach were particularly free from severe forms of food-sensitiveness.

At any rate, Woldman has devised a test in which a little phenolphthalein, dissolved first in alcohol and then in a little water, is drunk on an empty stomach. If the mucosa of the digestive tract is ulcerated, some of the phenolphthalein promptly goes through into the blood and then into the urine, where it can easily be detected. In many tests Woldman has found that the new procedure agrees well with roentgenologic reports indicating the presence of breaks in the gastro-intestinal lining, and in some cases the method proved to be very helpful. It may enable physicians to tell when a deformity in the duodenum means the presence of an open ulcer, and it may be useful in telling when an ulcer has healed and the patient can be freed from dietary restrictions.

If, as now appears, a negative test can rule out the presence of cancer in the digestive tract, we will have a most valuable tool added to our diagnostic kit.

Everyone will probably now start using the test, and within a few months we ought to know how useful and how trustworthy it is.

Walter C. Alvarez, Rochester.

SUGGESTIONS FOR A NEW SCIENCE

A NEW and promising field for research now awaits opening up and cultivation, and this is the art of so treating certain foods like beans and cabbage that they will lose much or all of their harmfulness to many sensitive men and women. That something can be done along this line is suggested by a number of facts:

As everyone knows, cooking greatly improves the digestibility of a number of foods, not only by breaking up cellulose partitions but also by altering irritant or somewhat poisonous substances. Thus apples, which when eaten raw cause discomfort in a large percentage of persons, when cooked appear usually to be harmless. During a study of food-sensitiveness made by Hinshaw and me, we met a number of intelligent persons who said that so far as they were concerned, the paring of certain foods, such as cucumbers, or the soaking of them in water or vinegar, or the cooking of them in a certain way, would render them harmless. Why shouldn't more research be done along this line, and might it not be possible to find some way of destroying or dissolving or altering chemically the substances in beans and other foods that cause them to be flatulent?

Curiously, cooking brings out the harmful properties

of cabbage, and many persons who can digest cole slaw cannot handle cooked cabbage with any comfort.

Search should be made for ways of "denaturing" the proteins or other substances in foods which injure so many allergic persons. It is known, for instance, that the evaporation or drying or fermenting or even the boiling of milk makes it less harmful to some persons who otherwise could not drink it with comfort. Some wheat sensitive persons are able to take bread which has been largely dextrinized in the oven. Recently the unpleasant taste has been removed from soy beans. In ages past primitive savages in Africa learned how to take the poison out of the cassava root. Cooking tends to destroy the Solanin which sometimes severely poisons persons who eat raw sweet potatoes. In recent years chemists have learned to take most of the caffeine out of coffee. In the manufacture of cocoa the fat is removed. Many other examples of such refining of foods might be mentioned. One of the commonest of these processes is the bolting of white flour with the mechanical removal of the husk and also of the germ which contains oils that interfere with the keeping qualities of the flour.

It would seem that after having made such good beginnings in the way of improving the digestibility of foods and in removing toxic substances, man ought to be able to go on to even greater accomplishments.

Walter C. Alvarez, Rochester.

NEW LIGHT ON THE NATURE OF THE GASTRO-INTESTINAL FERMENTS

OF great interest to the gastro-enterologist is the article on "The formation of enzymes" by Northrop in the January, 1937, number of "Physiological Reviews" (page 144). As will be remembered, Northrop was the first man to obtain crystalline pepsin, and, with Kunitz, to crystallize trypsin. These substances have now been shown to be proteins. Northrop has been much interested in studying those slight changes in an inactive protein which result in the formation of an active enzyme. Under certain conditions the reaction is autocatalytic; in other words, some enzymes possess the power to form themselves from inert proteins.

Already some insight has been gained into the chemistry of the activation of pepsin. Thus, it has been shown that acetylation of the primary amino groups of pepsin has no measurable effect on its activity, while acetylation of other groups, and probably particularly tyrosine, or iodination of the tyrosine results in loss of activity.

Long ago Heidenhain and Kühne showed that freshly secreted pancreatic juice is inactive, and it was assumed that the enzymes were secreted in an inactive form. The formation of the active enzymes from inactive pancreatic juice or from inactive extracts of pancreas has been studied extensively, but until recently the reports in the literature were confusing and contradictory. Northrop showed that this was due to the fact that the work had all been done with crude preparations containing mixtures of the proferments and inhibitors. Since small admixtures of these inhibitors markedly can influence the processes of activation, the experiments would never come out the same way until the proferment was isolated and crystallized several times in succession. When in this way the

chymotrypsinogen is freed from inhibitor and trypsinogen, its activation by trypsin becomes a clear-cut and reproducible reaction. The rate is proportional to the trypsin concentration and also to the chymotrypsinogen concentration.

The rate of activation by trypsin is affected by the acidity of the solution in the same way as is the rate of digestion of other proteins by trypsin, so that the reaction appears to be analogous to ordinary protein hydrolysis. There is one striking difference, however, in that, so far as Northrop and his coworkers have been able to determine, nothing is split from the chymotrypsinogen molecule although there is an increase of five amino groups per mol. The formation of the active from the inactive form of chymotrypsin, therefore, appears to be due to the opening of a peptide ring.

As in the case of chymotrypsinogen, the activation of trypsinogen changes markedly after the purification and crystallization of the substance. Amorphous preparations are stable in solution and can only be activated by the addition of kinase, large quantities of trypsin, or concentrated solutions of magnesium or ammonium sulfate. After crystallization, however, the inactive protein changes rapidly into the active enzyme as soon as it is dissolved in a neutral solution. The reason for the absence of such change in amorphous preparations of the proferment is that they contain traces of an inhibitor which prevents the autocatalytic reaction from taking place. As soon as this inhibitor is removed by crystallization the addition of a minute quantity of trypsin will start the activation reaction, which then proceeds autocatalytically.

Langley showed that pepsin existed in the gastric mucosa in a form which differed from that of the active enzyme in that it was much more resistant to alkali. Herriott has recently succeeded in isolating and crystallizing this substance. It has no proteolytic activity but in slightly acid solution it becomes converted into active pepsin. The reaction at pH 4.65 is autocatalytic and hence is caused by pepsin itself. So far as is known, pepsin attacks only peptide linkages so that there is reason to believe that the rupture of one or more peptide links in the protein proferment leads to the formation of the active enzyme.

While on the subject of the digestive ferments, the reader would do well to turn back to the eleventh volume of "Physiological Reviews" to a most interesting article by Waldschmidt-Leitz on "The mode of action and differentiation of proteolytic enzymes." He divides the proteolytic enzymes into proteinases and peptidases, and the proteinases into pepsinases, trypsinases, and papainases. According to Northrop (*Naturwissenschaften*, 11:713, 1923) the pepsinases react with protein cations, the trypsinases, with anions. The papainases appear to react with isoelectric protein. The peptide-splitting enzymes can be divided into carboxypolypeptidases and aminopolypeptidases, dipeptidases, and amino-peptidase or prolinase, according to the point of attack.

It is interesting to see how much exact information is now being obtained as to the chain-like way in which one ferment after another breaks down the protein molecule into simpler and simpler forms. Evidence accumulates to show that the action is a fairly simple chemical one and not a surface phenomenon as was once thought.

W. C. Alvarez, Rochester.

Abstracts

THE AMERICAN CONGRESS ON OBSTETRICS AND GYNECOLOGY

The first American Congress devoted to a consideration of medical, nursing and other problems associated with human reproduction will be held in Cleveland, Ohio, from September 11 to 15, 1939, inclusive. It will be designated as The American Congress on Obstetrics and Gynecology. The promotion and sponsorship of The Congress has been delegated to the American Committee on Maternal Welfare, Inc. The latter includes the following organizations in its membership:

American Association of Obstetricians, Gynecologists and Abdominal Surgeons

American College of Surgeons
American Gynecological Society
American Hospital Association
American Nurses Association
American Protestant Hospital Association

American Medical Association
Section on Obstetrics and Gynecology
American Public Health Association
Central Association of Obstetricians and Gynecologists

Chicago Maternity Center
Maternity Center Association of New York

National Medical Association
National League of Nursing
National Organization for Public Health Nursing

New England Obstetrical and Gynecological Society
Pacific Coast Society of Obstetrics and Gynecology

Southern Medical Association
U.S. Bureau of the Census
U.S. Children's Bureau
U.S. Public Health Service.

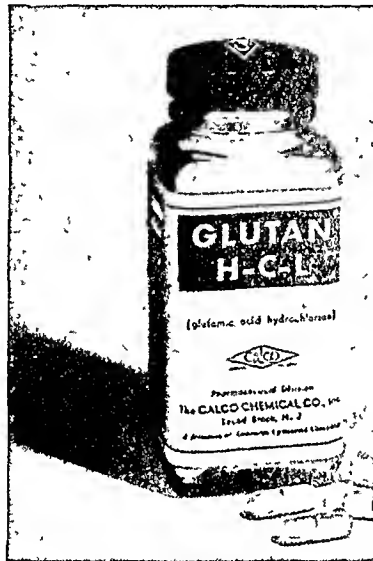
The purpose of this Congress is to afford opportunities for discussing and publicizing the problems associated with human reproduction and the health of women and new born babies. The value of more generally disseminated knowledge about the processes and problems of human reproduction and of the special diseases of the female generative organs and the new born is important in the maintenance of public health and therefore the interest of woman's welfare extends not only to the medical profession but to associated groups, including nurses, public health officials, hospital administrators, eugenists and many others.

Problems develop with the expansion of knowledge and these can be discussed most effectively at a meeting where many viewpoints can be intelligently discussed. Congresses,

international and national, afford the means of presenting and discussing the advances in various fields of science and bringing them to public attention. Obstetrics and gynecology in particular demand that wider association with allied groups, aside from the practitioners of medicine, which is so essential to the progress and welfare of the public. For these reasons the scope of the projected Congress has been extended beyond

that of similar assemblies held in the past and will devote much attention to the wider public welfare aspects of problems which have been considered frequently of purely medical interest.

The last International Congress of Obstetrics and Gynecology was held in Amsterdam, Holland, in May of the present year. Its success stimulated a desire to hold a subsequent one in five years in another European country. It is felt that the difficulties asso-



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ciated with an international assembly, such as languages, expense, long distance travel, and limited participation, lack of common interest, call for a regional gathering in which opportunities for more general discussions would prevail. The proposed American Congress will therefore be modeled on different lines and include participation not only by medical groups but by those devoted, as already stated, to nursing, public health and institutional administration. The program will provide morning, after-

noon and evening sessions, the details of which will be announced subsequently.

National, sectional and local specialist societies have approved the Congress and have made contributions for its support. It is desired that a wider representation be secured through the medium of contributing memberships, the cost of which has been placed at five dollars. Application may be made at the office of the Congress, 650 Rush Street, Chicago, Illinois. Early application is desirable and will serve as

an indication of personal interest in the success of the undertaking.

In addition to the scientific sessions it is planned to provide for several evening meetings at which speakers of prominence will discuss the broader aspects of the subjects for the lay public. There will also be prepared a comprehensive exhibit — scientific, educational, technical and commercial, which should add greatly to the general interest of the Congress.

Cleveland is well adapted for a meeting of this kind. There are ample hotel facilities and the city is admirably located. The municipal auditorium, with suitable rooms for all types of meetings has been secured. Cleveland is a large railroad center and provides adequate transportation facilities, rendering access to the Congress easy from all parts of the United States and Canada.

The officers and committees thus far selected are as follows:

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Sara B. Place, Chicago, Illinois, Secretary.

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 120 cal.
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Vomiting of pregnancy is a disturbance in carbohydrate metabolism. Hence the treatment by small carbohydrate meals at three-hour intervals. Karo added to foods and fluids prevents glycogen depletion and ketosis.

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CLEVELAND Arrangements Committee

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FRIEDENWALD, JULIUS AND FELDMAN, MAURICE.

"Medical Aspects of Carcinoma of the Colon with Special Reference to the Early Diagnosis." *Southern Med. Jour.*, 31:1078-1087, Oct., 1938.

Carcinoma of the colon grows slowly, involves other structures relatively late, and offers a good prog-

nosis if radically removed early in its course. While some cases are silent in their symptomatology and others with symptoms are neglected by the patients themselves there are a number of cases which may be recognized earlier by the physician who will carefully consider apparently trivial complaints. While the greatest incidence of the disease is between the fiftieth and sixtieth years it may occur between the ages of ten and thirty and also in the very aged. Loss of weight when present is quite significant. Any unexplained progressive secondary anemia should always suggest the possibility of a colonic

malignancy. Dyspeptic symptoms usually vague and intermittent at first, evidence themselves in the form of anorexia, eructations, fullness, and flatulency, with nausea and vomiting in obstructive cases. Toxemia and cachexia usually occur late but in cases involving the cecum marked toxemia may be a relatively early symptom. Unexplained weakness and exhaustion are also often found.

Of especial significance is an alteration in the character of the stool. Constipation is the rule and a pre-existing constipation usually becomes more pronounced. Diarrhea may occur and should arouse particular suspicion if it alternates with constipation. The stool may contain mucus, blood, or pus and is often quite offensive. Unless there is obstruction the pain is usually mild and intermittent and often relieved by the expulsion of flatus. Obstruction is evidenced by increasing constipation and pain.

Profuse hemorrhage is rare but occult blood and bloody mucus are quite common. A palpable mass is a less frequent and rather late finding, usually difficult to demonstrate. It is very important to remember that no examination in case of suspected malignancy of the colon can be complete without a digital, sigmoidoscopic, and thorough X-ray study. The latter should include a barium enema, a barium meal. (In non-obstructed cases) and possibly air insufflation, and a single examination should not always be relied upon as final. (Rather detailed technique and interpretation are given).

In differential diagnosis regional ileitis, tuberculosis, ulcerative colitis, amebiasis, diverticulitis and benign strictures and growths must be considered.

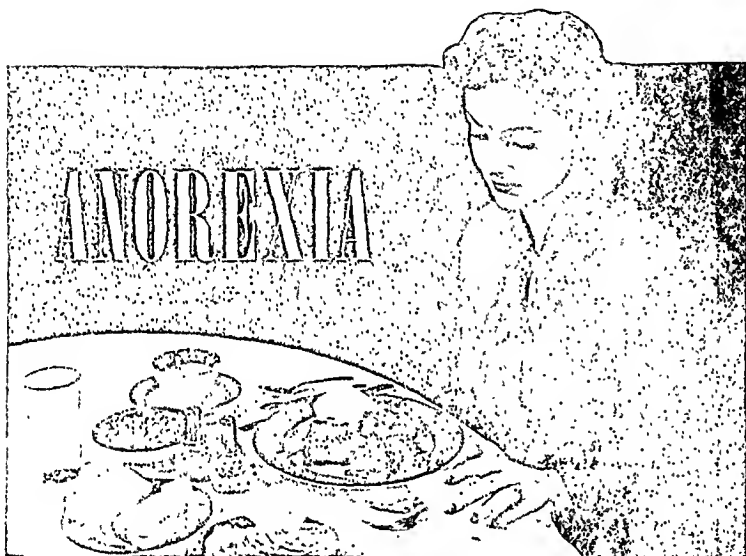
Since surgery offers the only hope for a cure and since it must be done early to be successful a careful investigation for an evaluation of the symptoms presented is urged.

J. Duffy Hancock, Louisville.

READ, JOSEPH C.

"Review of One Hundred Cases of Acute Ruptured Peptic Ulcer." *Southern Surgeon*, 7:436-443, Oct., 1938.

This interesting series confirms most of the generally accepted views regarding ruptured ulcers. Ninety of the patients had sudden severe epigastric pain, sixty-three were nauseated and forty-five vomited. Although only twelve had previously consulted a physician for their symptoms ninety-two gave a history of some type of dyspepsia. Ninety-seven of the patients were males showing the usual preponderance of ninety per cent or more. Eighty-two of the cases occurred between the ages of twenty



LOSS of appetite without apparent cause is often due to vitamin-B₁ deficiency. Extra-dietary supplies of vitamin B₁ must be administered to break the vicious circle of relative increase in carbohydrate intake (because of distaste for other foods), increased vitamin-B₁ deficiency, increased anorexia. Berocca, crystalline vitamin B₁, 'Roche,' is speedily effective as a diagnostic and therapeutic measure. Dosage: for diagnosis (therapeutic test)—1 to 2 mg. Berocca, parenterally; for treatment—2 to 5 mg. Berocca a day, orally.

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RECENT ADVANCES IN THE SCIENCE OF NUTRITION

III. Some Attainments in the Fields of Vitamin A Research

● During the twenty-five years since its discovery, vitamin A has been the subject of much intensive research, first by the biochemist and physiologist, and later by the clinician and organic chemist. It may be of interest to describe briefly several of the achievements made in these various fields of research on vitamin A.

It has been found that vitamin A is unique among the vitamins thus far discovered. It is apparently the only vitamin produced solely by animal metabolism from precursors—certain carotenoid pigments—which are themselves solely the products of plant metabolism. The structure of the vitamin has been established and checked by syntheses of closely allied forms and probably of the pure vitamin itself (1).

Physiological and clinical researches have provided explanations of the mode of absorption of the vitamin and the mechanisms of transport and storage in the body (2). The specific pathological effects of varying degrees of vitamin A deficiency in humans have been extensively studied. Many of the older ideas concerning specific effects of vitamin A on man have been confirmed; some of the older beliefs have been dispelled (2).

Recent years have also brought improvements in assay methods for vitamin A (3). Common American foods have been sur-

veyed and their vitamin A values tabulated (4). Last but not least, authoritative estimates are at hand as to the quantitative requirements of children and adults for vitamin A (5). Such, in brief, are only a few of the important additions which have been made to our knowledge of this essential dietary factor. Today, students of nutrition favor the practice of "protective nutrition" in which the individual is maintained upon a diet calculated to supply all known dietary essentials—vitamin A included—in optimal amounts insofar as these amounts may be known. In specific instances, such dietaries must be supplemented by vitamin-rich materials. However, the prime consideration is to provide a properly formulated basic diet. In this connection, commercially canned foods are worthy of mention.

Modern canning procedures are practically without effect upon the vitamin A values of raw foods (3). The commercially canned varieties of foods prized for their vitamin A contents, therefore, lend themselves admirably to the formulation of protective diets. Not only because of their contributions of vitamin A, but also because of their ready availability, convenience and economy, these commercially canned foods provide one of the most valuable means whereby the American public may secure an optimal supply of the important dietary essential, vitamin A.

AMERICAN CAN COMPANY

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1 1938 J A M A. 110, 1748

2 1938 Ibid 111, 144

1938 Ibid 110, 2072

3 1938 Ibid 111, 245

4 1937 U S D A Bur of Home Econ, Misc. Pub 275

5 1934-1935. Amer Pub Health Assn Year Book 25, 69

We want to make this series valuable to you, so we ask your help. Will you tell us on a post card addressed to the American Can Company, New York, N. Y., what phases of canned foods knowledge are of greatest interest to you? Your suggestions will determine the subject matter of future articles. This is the forty-second in a series, which summarize, for your convenience, the conclusions about canned foods reached by authorities in nutritional research.



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and fifty, the youngest patient was eighteen and the oldest seventy-four, and four had had previous perforations. No seasonal influence was apparent and there was no history of trauma or straining in any instance. Gastric and duodenal ulcers were about equally divided.

All of the patients appeared acutely ill and eighty-one showed moderate or severe prostration. Everyone had some degree of upper abdominal rigidity and ninety-nine showed tenderness there. Rebound tenderness was usual and abdominal distention rare. Eighty-five per cent of the cases tested for obliteration of liver dullness gave positive evidence of this most impor-

tant sign. While there was considerable variation in the temperature, pulse, respiration, and white count the averages respectively were 98.4°, 92, 24, and 14,300 with 83% polys. X-ray examinations were not as conclusive as might be expected probably because of faulty technique.

The most common conditions to be considered in differential diagnosis are gall stone colic which is more localized in the right upper quadrant and accompanied by more restlessness, acute pancreatitis which presents profound shock and symptoms out of proportion to the physical findings, and acute appendicitis which usually does not have the extreme upper ab-

dominal rigidity but does show more frequent emesis.

All of the patients were subjected to surgery which was conservative (simple suture with or without excision of the ulcer) in ninety of the cases, and this plan is believed to give the lowest mortality in the hands of the average good surgeon. Post-operative measures included the use of the Levin tube, with or without suction, Fowler position, morphine, glucose and saline intravenously and subcutaneously, and warm drinks by mouth after several days.

By far the most frequent complication and cause of death was general peritonitis. Subphrenic abscess with or without peritonitis was the next most important factor in mortality. While others have reported better results with the use of spinal anesthesia the cases in this series showed no especial advantage over ether.

Thirty of the patients died, a mortality fairly in accord with other reports. The significant fact to be emphasized, however, is the direct relationship between mortality and time of operation the greatest increase becoming apparent after the perforation has been present more than nine hours. Early recognition of the disease by the family physician and prompt action by the surgeon are indispensable if an appreciable lowering of mortality is to be expected.

J. Duffy Hancock, Louisville.

COPELAND, SIDNEY MARVIN.

"The Clinical Aspects of Gastric Hemorrhage." *Southern Med. Jour.*, 31:1075-1078, Oct., 1938.

A bleeding ulcer is never to be lightly regarded. It carries a very definite mortality which is not always borne in mind. A good rule to remember is that the older the patient, the longer the history, and the more severe the symptoms, the more seriously is the hemorrhage to be considered. While the prognosis when hemorrhage is the first symptom of an acute ulceration is favorable, the ulceration may be quite chronic and symptomless until there is hemorrhage in which instance the outlook is not so promising. Mild cases where there are repeated small hemorrhages can usually be controlled without fatality whereas the massive ones, which may or may not be repeated, carry an inevitable mortality under the best plans of treatment.

Patients with bleeding ulcers should be hospitalized. Shock should be combated by morphine and glucose. The latter should be given intravenously preferably combined with a acacia rather than saline solution in order not to disturb the normal viscosity of the blood. Although there is some difference of opinion regarding the use of transfusions in massive hemor-

Strained Vegetables And Fruits Supply Infants With Significant Amounts of Minerals



Of the minerals which occur in the human body, those known to play physiological roles and to be indispensable for normal nutrition include sodium, potassium, calcium, magnesium, chlorine, iodine, phosphorus, sulphur, iron, manganese, copper and zinc, and apparently cobalt. It has been demonstrated that the total absence of any of these elements from an otherwise adequate diet will cause characteristic failure of nutrition in experimental animals.

Hanning reports that rapid curing of nutritional anemia in rats resulted from feeding adequate amounts of vegetables, or the equivalent quantities of iron and copper salts. (1)



Iron is not contained in either cow's milk or human milk in amounts adequate to meet the requirements of a normal infant. (2) Rapid growth and increased production of blood in the newborn infant depend upon a reserve of iron in the liver. A 2-ounce feeding of Gerber's Strained Prunes supplies 2.8 milligrams of iron. A 2-ounce feeding of Gerber's Strained Liver Soup supplies 1.6 milligrams of iron. (3)

In a study by Glazier in which 231 infants were observed he concludes, "A full diet which includes cod liver oil, orange juice, cereals, egg yolk, strained fruits and strained vegetables, given during the second and third months of infancy, produces a better state of nutrition and better food and bowel habits, because: it contains more nearly adequate amounts of vitamins A, B, C, and D; it provides bulk to the stool, eliminating an important cause for constipation in infants; and it accustoms the infant to solid food early in life, thus improving its food habits." (3)

Care is taken to conserve all minerals which are present in the raw products used in Gerber's Strained Foods. Their calcium, phosphorus and iron content are measured by analysis of samples selected from the entire season's pack, and averaged. These analyses are supplied on request.

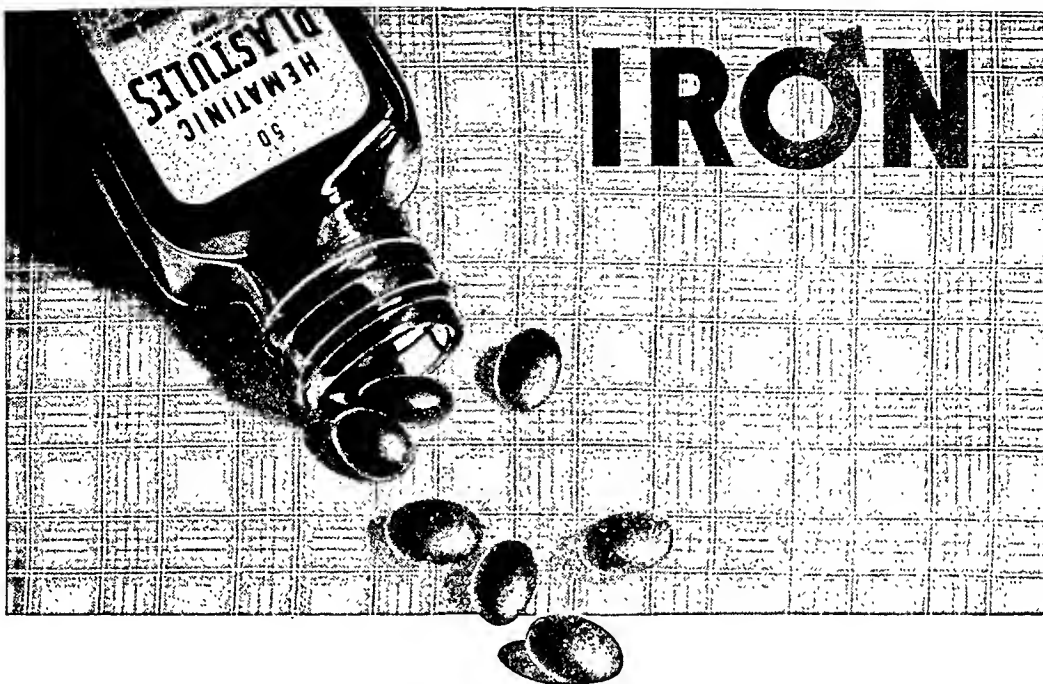
Free on request: Analyses of mineral and vitamin content of Gerber Strained Foods. Also recent reprints. Gerber Products Co., Dept. 3311, Fremont, Michigan. (In Canada, Gerber's are grown and packed by Fine Foods of Canada, Ltd., Tecumseh, Ont.)

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APRICOT AND APPLE SAUCE... BEETS
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LIVER SOUP WITH VEGETABLES... PEAS
PRUNES... SPINACH... TOMATOES
VEGETABLE SOUP

1. The Value of Some Common Vegetables in Curing Nutritional Anemia in the Rat, Flora Hanning, Michigan State College of Agriculture and Applied Science, Jour. Am. Dietetic Assn., March, 1934.
2. Strained Fruits and Vegetables in the Feeding of Infants, Council on Foods, Jour. Amer. Med. Assn., 103, 1259 (1937).
3. Advantages of Strained Solids in the Early Months of Infancy, Manuel M. Glazier, M.D. Jour. Ped., 3, 883 (1933).



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More than two weeks' treatment with Fifty Hematinic Plastules Plain may be obtained at an average cost of less than one dollar.

Each Hematinic Plastule Plain provides five grains of ferrous iron and the vitamin B complex of concentrated yeast.

A marked improvement attends the use of Hematinic Plastules in cases of hypochromic anemia. They are well tolerated and easy to take.

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rhage it seems more reasonable to use them. Nothing should be given by mouth the first twenty-four hours, only small amounts of ice water and perhaps non-residue fluids during the second twenty-four, afterwards a modified sippy diet if improvement continues. The use of coagulants such as snake venom, Vitamin C, and coagulin is harmless but of unproven value. Gastric lavage is indicated only for massive dilatation and the solution then used should be ice water.

Immediate surgery is indicated only for massive repeated hemorrhages. The indications for subsequent elective surgery are debatable. While it does not offer absolute protection against future hemorrhage it does

offer it to a high degree, and Eusterman and Balfour are quoted as saying that the possibility of serious consequences from subsequent bleeding in cases in which no operation is performed is greater than the risk of surgery plus its failure to protect against further hemorrhages.

J. Duffy Hancock, Louisville.

PORTIS, SIDNEY A.

Medical Treatment of Patients with Jaundice. Illinois Med. Jour., 74:249-253, Sept., 1938.

The type of jaundice most commonly seen is that which is associated with bile tract disease and gives a biphasic van den Bergh reaction with an icterus index above 20 as a rule.

Obstruction of the bile passages was previously thought to be the most common cause of jaundice, but increasing knowledge of liver disease has shown that toxic and infectious jaundice are the more common forms. By far the most common cause for the infectious and toxic type is cholecystitis with some corresponding degree of hepatitis.

The physiologic methods of evaluating liver function are for clinical purposes three in number: first, the amount of bilirubinemia; second the cholesterol ester fraction of total cholesterol; third, the total serum protein and albumin globulin ratio. The degree of bilirubinemia is expressed as the icterus index. Approximately 70% of the cholesterol in the blood is in the form of the ester, and when it goes below 50%, it is indicative of definite liver damage. The normal relation of albumin to globulin in the blood stream is four or three to one. In cases of liver damage this may be reduced to a one to one ratio or even to a one to two basis. It must be remembered that in protein loss, particularly with nephrosis, a similar albumin globulin ratio may exist.

Ten per cent glucose in saline or water intravenously is an ideal way to supply the liver with sufficient carbohydrate. There is no indication for the use of insulin in non-diabetics.

In the presence of jaundice one should withhold surgery until it subsides to a near normal level and other physiological methods indicate evidence of an increased liver reserve. All patients with gall stones, unless they are poor surgical risks, should be treated surgically. There is no urgency for surgery in a gradually increasing jaundice, especially if one is fairly certain it is not an obstructive or mechanical type of jaundice.

In treating patients with liver disease and associated jaundice, conservatism should be the better part of one's valor.

Hanes M. Fowler, Fort Wayne.

DANN, MARGARET AND COWGILL, GEORGE R.

Influence of Diarrhea on the Vitamin B₁ Requirement. Arch. Int. Med., v, 62, 136-150, July, 1938.

This continues the quantitative studies of B₁ requirement carried on by Dr. Cowgill and his coworkers. Anorexia has been chosen as an indicator of B₁ deficiency because it appears early before there have been grave changes in animal metabolism. Previous experiments demonstrated that the B₁ requirement of different species is a function of body weight and metabolic rate, that exercise, fever and diuresis increase B₁ need.

In this study young mongrel dogs were given an excess of B₁ to satur-

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Provides you with an improved formula, a combined salicylate-iodide effect together with protective alkali buffers.

Provides your patient with an acceptable, effervescent form, easy to take, quickly effective, well tolerated.

THE FORMULA:

Each tablet contains

Sodium Salicylate	7½ grs.	Citric Acid	17 grs.
Sodium Iodide	1 gr.	Sodium Bicarbonate	.25 grs.

Note quick relief from pain and muscle spasm following the use of Salici-Vess. Tubes of 30.

Also available—Aspir-Vess (aspirin with alkali buffers); and Alka-Vess (for safe alkalization).

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A doctor writes, "Would you kindly tell me from what sources the materials used in making Knox Gelatine are obtained? I am especially interested in whether or not it is all beef, all pork, all sheep, or a mixture of proteins from different animals; also is the manufacture constant as to the ingredients used? This is very important to me as I want to use it for special diets in allergic cases, and for this purpose the exact sources of a food must be known and unvaried."

A good example of a CONCENTRATED Knox Gelatine Recipe:

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Knox Gelatine is scientifically prepared from carefully selected long, hard, shank *beef bones only*. Twenty-one control and laboratory tests are made throughout the process of its manufacture. As far as we know, no case of allergy has ever been traced to the use of Knox Gelatine.

—THE KNOX MILK STIR—

Place the contents of 4 envelopes of Knox Gelatine in an ordinary drinking glass. Add 4 ounces of cold milk and allow to soak for five minutes. Add 2 more ounces of milk and stir until thoroughly soaked. Then place glass in small cooking kettle of hot water until gelatine milk mixture is thoroughly dissolved. Add 2 more ounces of cold milk, which will bring the temperature to a satisfactory warm drink of about body heat. A tablespoonful of prune juice or a few drops of any bland flavor like vanilla may be added.

Total: 8 oz. liquid—about 250 calories

Sample and useful Dietary Booklets on Request Write Dept. 475

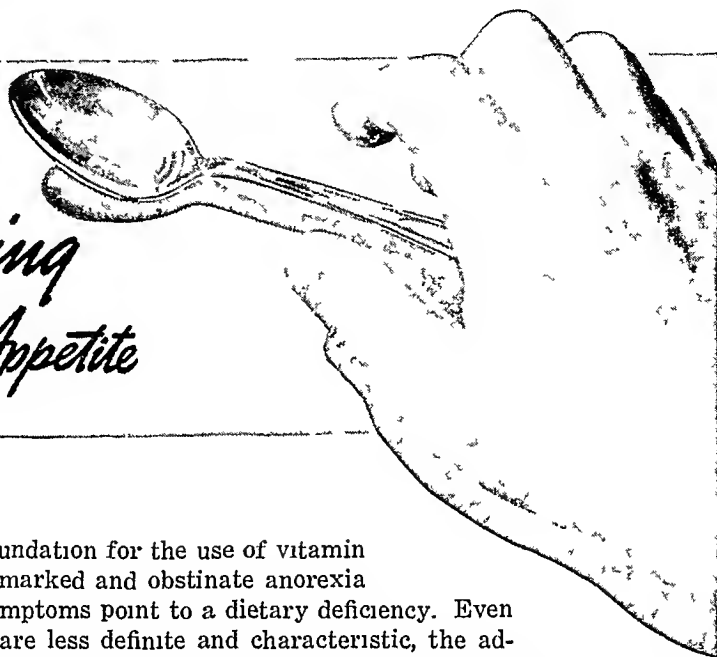


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Because Knox Gelatine is 85% protein in an easily digestible form—because it contains absolutely no sugar or other substances to cause gas or fermentation, Knox Gelatine should not be confused with factory-flavored, sugar-laden dessert powders. Knox is 100% pure U.S.P. gelatine. Knox Gelatine has been successfully used in the dietary of convalescents, anorexic, tubercular, diabetic, colitic, and aged patients.

KNOX SPARKLING GELATINE
IS PURE GELATINE—NO SUGAR
KNOX GELATINE LABORATORIES
JOHNSTOWN, NEW YORK

Arousing the DORMANT Appetite



• There is a sound foundation for the use of vitamin B₁ in cases in which marked and obstinate anorexia and accompanying symptoms point to a dietary deficiency. Even when the symptoms are less definite and characteristic, the administration of vitamin B₁ serves a doubly useful purpose: If the results are favorable they indicate the probability of a previous shortage of vitamin B₁; if they are negative they help to clear up the diagnosis. Through the synthetic production of vitamin B₁—Betaxin—this essential food factor is obtainable in a pure, stable, crystalline form. Betaxin is available in different dosages for peroral use and intramuscular injection.

HOW SUPPLIED:

Tablets of 0.1 mg., 0.5 mg., and 1 mg., bottles of 50; tablets of 5 mg., bottles of 25.

Elixir containing 5 mg. in each fluidounce, alcohol 9%, benzoic acid 0.1%, bottles of 8 fluidounces and 1 gallon.

Ampules of 1 mg. (1 cc.), boxes of 10 and 100; ampules of 10 mg. (1 cc.), boxes of 5; vials of 100 mg. (10 cc.).



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charts giving the incidence of intestinal parasites according to age, sex, and race groups, also a chart showing the incidence in food handlers in Dallas, Texas.

Endameba histolytica was found to be the most prevalent pathogenic organism, being found in 97 persons for an incidence of 3.46%.

Hanes M. Fowler, Fort, Wayne.

DUTTON, L. O.

The Relationship Between Allergy and Organic Pathology of the Appendix. Texas State Jour. Med., 34:363-366, Sept., 1938.

The author presents two case re-

ports which substantiate his conception that allergic reactions in the appendix are probably a common etiological factor in the development of both acute and chronic appendicitis.

Mild allergic reactions can explain some of the pathologic changes found in the chronic appendix, and also the clinical manifestations of the disease. This is particularly true of the profound systemic symptoms that cannot be explained on the basis of the histologic findings alone. The edema incident to the allergic reaction certainly could account for all of the stasis of the lumen contents that would lead to damage to the mucosa. The irreversible necrosis of the allergic reaction

certainly would offer ample opportunity for bacterial invasion to occur. In other words, an easily understood initiating lesion is certainly an integral part of the allergic reaction. The author believes that by the combination of the allergic and the ineffective in the consideration of appendicitis, many of the unanswered questions concerning the disease may be answered.

Hanes M. Fowler, Fort Wayne.

HENCH, PHILIP S.

Effect of Spontaneous Jaundice on Rheumatoid Arthritis. British Med. Jour., pp. 394-398, Aug. 20, 1938.

Jaundice involves a physiological reaction which is antagonistic to the continuation of active symptoms of rheumatoid arthritis and primary fibrositis. With the onset of any one of several types, rather dramatic remissions in rheumatic symptoms, lasting from three to 104 weeks, occurred in nineteen cases of rheumatoid arthritis, in nine of primary intra-muscular or peri-articular fibrositis, in two of lumbo-sacral and sciatic pain, and in one of secondary hypertrophic arthritis of the hips. Remissions averaged (roughly) from two to three times the average duration of the jaundice and affected symptoms of active disease; residual articular thickening and disability from deformity were unaffected.

The phenomenon depends more on the quantity than on the quality (or type) of jaundice, a certain intensity of jaundice being required. Several methods involving the administration of various components of bile and the production of artificial jaundice and induced hyperbilirubinemia are being used in an attempt to reproduce the phenomenon.

Hanes M. Fowler, Fort Wayne.

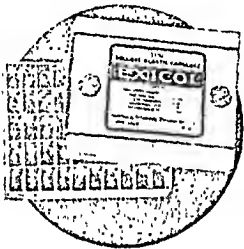
CONWAY, F. M.

Impalement of the Rectum. S. G. O., Vol. 66, No. 2, pp. 222-226, Feb. 1, 1938

Impalement of the rectum is an unusual type of injury requiring immediate surgical treatment. Most of the reported cases have occurred following a fall from a hay loft, striking the handle of a pitch fork. Impalement may be the "pure type" in which the impaling object passes through the rectal wall from within outward, or the "atypical type" in which the wall of the bowel is perforated after the impaling object passes through the soft tissues of the perineum. In either type other injuries to such organs as the bladder, small intestine, or kidney may be found. Fistulae and abscesses may develop along the course of an atypical impalement.

The symptoms may not be marked

Choosing a Happy Medium . . .



EXICOL

(Oleic Acid and Bile Salts)

The most recent researches* again emphasize the marked fat-intolerance displayed by patients suffering from gall bladder disease, and the satisfactory therapeutic results on a low fat diet and bile salts. Contrary to recent advocates of high fat therapy, it is pointed out that overstimulation of the gall bladder, produced by such high fat diets is undesirable.

Exicol, containing a small quantity of fatty acid and bile salts, offers a solution to the controversial problem of biliary tract therapy. It is the most rational therapeutic agent in biliary disorders because—

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*Amer. J. Digestive Diseases, Vol. 5, No. 6, p. 348, August, 1938.

**J. Lab. and Clin. Med., 19:567, 1934.

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A MODIFICATION OF THE ANSON AND MIRSKY HEMOGLOBIN METHOD FOR THE DETERMINATION OF PEPSIN IN GASTRIC DRAINAGE	J. M. Beazell, M.S., M.B., C. R. Schmidt, M.S., M.D. and A. C. Ivy, Ph.D., M.D.
DIABETES MELLITUS AND PEPTIC ULCER. A CLINICAL STUDY OF NINE CASES	Robert E. Rothenberg, M.D. and Ira Teicher, M.D.
END RESULTS AFTER GALL BLADDER OPERATIONS, WITH AN ANALYSIS OF THE CAUSES OF RESIDUAL SYMPTOMS	S. G. Meyers, M.D., D. J. Sandweiss, M.D. and H. C. Saltzstein, M.D.
MYCOTIC INFECTIONS OF THE STOMACH	Carl Bearse, M.D., F.A.C.S.
STUDIES IN CALCIUM METABOLISM: II. FURTHER CONTRIBUTIONS TO THE COMPARATIVE STUDIES OF THE PHYSICO-CHEMICAL PROPERTIES OF THE GLUCONATE AND CEVITAMATE OF CALCIUM AND OF VITAMIN C	Simon L. Ruskin, M.D. and Raymond Jonnard, M.D.
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CARCINOMA OF HEAD OF PANCREAS WITHOUT JAUNDICE	Charles Haines, M.D.
CALCIUM GLUCONATE AND KAOLIN IN THE TREATMENT OF BACILLARY DYSENTERY	Bernard L. Greene, M.D. and Louis H. Block, M.D.
HUMAN AUTONOMIC PHARMACOLOGY. XVII. THE EFFECT OF ACETYL-BETA-METHYLCHOLINE CHLORIDE ON THE GALL BLADDER	Parcell G. Schube, M.D., Abraham Myerson, M.D. and Ruth Lambert, A.B.
DIGESTION AND ABSORPTION IN A MAN WITH THREE FEET OF SMALL INTESTINE	Edward S. West, M.D., John R. Montague, M.D. and Frederiek R. Judy, M.D.
MELANOSIS COLI IN A BOY AGED TWO AND ONE-HALF YEARS	John H. Willard, M.D. and Thomas J. Shutt, M.D.
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Nelson M. Percy, Chicago.

HINES, LAURENCE E. AND FITZGERALD, BERTRAM.

Splenomegaly of the Banti Type. Report of a case with postmortem observations four years after splenectomy. Arch. Path., 26-1, 155, July, 1938.

The authors report the case of a man who presented the Banti syndrome whose spleen was removed in 1932, at the age of 45, and who died four years later from hemorrhage

from the rupture of an esophageal varix. No obstructive lesion of the portal circulation was found at operation, and the liver showed no evidence of cirrhosis. The health of the patient during the subsequent four years was not improved. The anemia continued from repeated hemorrhages. He died, as stated above, from a severe hemorrhage. At autopsy but little more could be found to explain the evident continued hypertension of the portal vein. The liver showed but a mild degree of intrahepatic peri-portal fibrosis, but it was associated with narrowing of the portal channels, which the author believed had to be regarded as the obstructive mechanism in this case.

N. W. Jones, Portland.

FARRELL, J. I. AND LYMAN, Y.

Aseptic Uretero — Intestinal Anastomosis. S. G. O., Vol. 66, No. 3, pp. 657-662, March, 1938.

The author describes an aseptic method of uretero intestinal anastomosis in which a side to side suture is placed between the ureter and the submucosa of the bowel; the muscular layers having been pushed back. A loop of silk thread is then passed through the ureteral wall and the mucosa of the bowel at the points opposite those in the ureter. After the anastomosis is completed, using 00 chronic catgut sutures, the opening between the ureter and bowel is established by sawing through with the silk suture. The ureter is then clamped beyond the anastomosis and any leakage of the anastomosis is sutured over. The entire anastomosis is covered with the longitudinal muscle layer and peritoneum of the bowel.

The author points out several advantages of this method. They are: (1) no catheters, cautery or bowel preparation are necessary, (2) the two structures are firmly united before the opening is made, (3) a longitudinal opening larger than can be made by most methods may be made, (4) the bowel musculature is not cut and the circular layer acts as a sphincter for the ureter.

Four figures and a bibliography accompany the article.

Nelson M. Percy, Chicago.

CHESTNUT, NELSON H.

The Use of Pitressin in Common Duet Obstruction of the Gall Bladder by Biliary Calculi. Ill. Med. Jour., 73:475-481, June, 1938.

The author briefly reviews the anatomy and physiology of the gall bladder and biliary ducts and discusses the causes of obstruction of the common duct.

The case presented illustrates the presence of a biliverdin stone ob-

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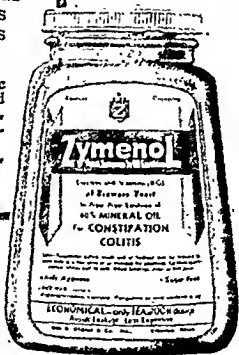
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1. "The Vitamin B Complex and Functional Chronic Gastro-Intestinal Malfunction: A Study of Two Hundred and Twenty-Seven Cases" by Dr. Borsook, Dougherty, Gould and Kreners, in Am. Jr. of Dig. Dis., June, 1938. Reprint available on request.
2. Relation of Vitamins to Enzymes, A. M. A. Journal, July 2, 1938, page 28.

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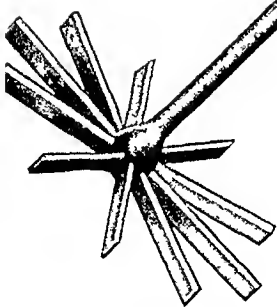
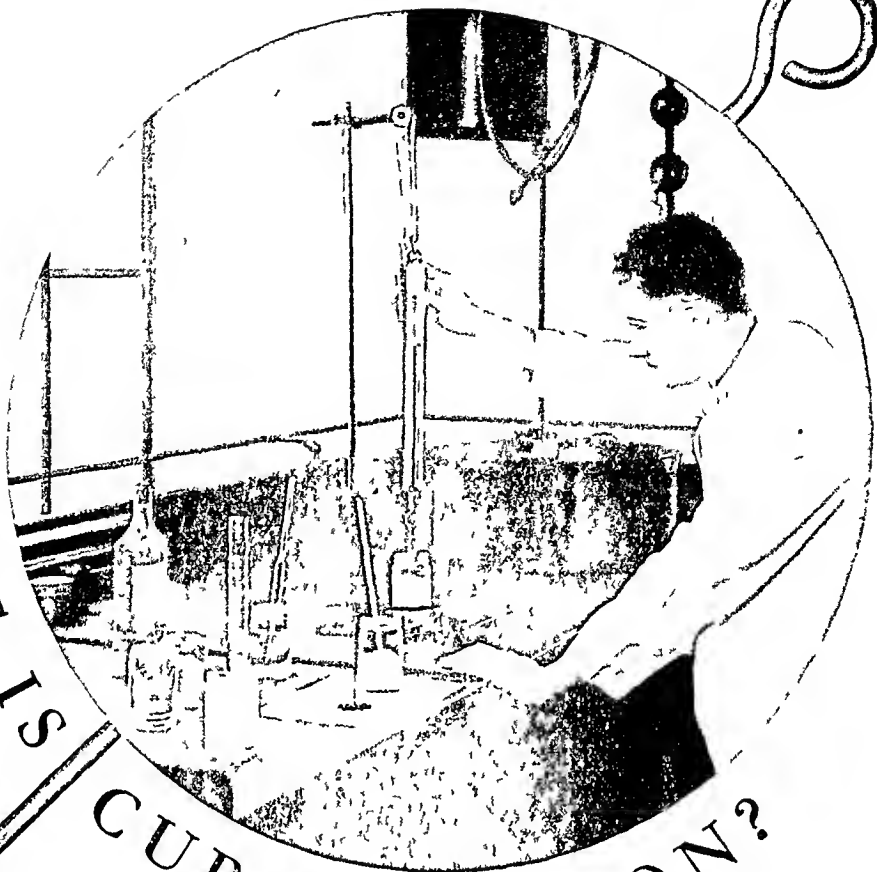
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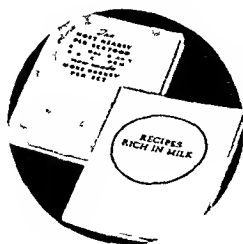
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structing the common duct, causing concentration of the bile and bile pigments with calcium deposit to make it opaque to X-rays. Injections of pitressin caused the stone in the ampulla to be dislodged and forced into the intestinal tract. Further injections of pitressin apparently caused more complete evacuation of the gall bladder by stimulating its contractions. These events were demonstrated by X-rays.

While admitting that no conclusions should be drawn from one case, the author suggests that the use of pitressin might well be considered in

the treatment of common duct obstruction by small biliary calculi.

Hanes M. Fowler, Fort Wayne.

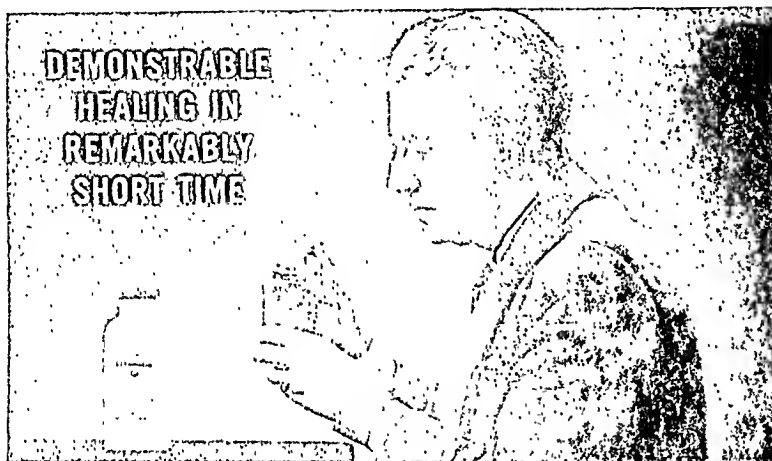
HOFRICHTER, C. H.

Experiences with Protamine Zinc Insulin. Northwest Medicine, 37:218-223, July, 1938.

Protamine zinc insulin is as effectual as standard insulin in the metabolism of carbohydrate, but much slower in exerting its influence substitution of protamine insulin for standard insulin is best done gradually. Mild cases of diabetes do well on protamine zinc insulin. Severe cases do well if one remembers not to rely

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GHOSH, JAHARLAL.

The Value of Gastric Analysis in Clinical Diagnosis. Jour. Indian Med. Assoc., 7:509-514, June, 1938.

Analysis of gastric contents is undoubtedly a valuable method of investigation of the dyspepsias but possibly its value is usually over-estimated. Achlorhydria with presence of definite amount of lactic acid in the fasting contents is highly of cancer of the stomach. Hyperchlorhydria in a suspected case of ulcer is merely an additional point in favor of the probability but not at all pathognomonic of the condition. The typical climbing curve when obtained in such a case is suggestive of duodenal ulcer. Analysis of gastric contents materially helps in the diagnosis of anemias and subacute combined degeneration of the cord. The results of gastric analysis should always be interpreted with due regard for the history, physical findings and results of other special methods of investigation.

Hanes M. Fowler, Fort Wayne.

MARSHALL, GEO. R. AND WOOD, O. L.

Ischio-Anal Abscess Caused by Oxyuris Vermicularis. Northwest Med., 37:180-182, June, 1938.

The anatomic importance of the crypts of Morgagni as a harboring recess for oxyuris vermicularis and ova is brought out, especially those crypts elongated by infection and trauma. Intractability to treatment has been associated previously with the possibility of an appendiceal involvement but the importance of the anal crypts in this condition has not been mentioned or stressed. Therefore, the importance of anoscopic examination in these cases and inspection particularly of the anal crypts, is emphasized.

A case of ischio-anal abscess containing oxyuris vermicularis is reported.

Hanes M. Fowler, Fort Wayne.



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A NATURAL LAXATIVE CEREAL



PHILLIPS, JOHN ROBERTS.

Severe Hemorrhage of Peptic Ulcer Origin." Southern Surgeon, 7:407-411, Oct., 1938.

The generally accepted view that severe hemorrhage of peptic ulcer origin rarely is fatal is probably incorrect. Statistics quoted showed a mortality of five to fifteen per cent of ulcer patients who bled while under hospital care. It is important to realize that hemorrhage in patients over forty years of age is much more likely to be fatal than in younger ones because increasing sclerosis of the blood vessels tends to hold open the vessels once erosion has occurred. Medical and surgical management are not competitive and the former should always be used first. If, however, the bleeding persists or recurs in massive quantities within a few days, and especially if the patient is past forty, immediate operation is imperative. As anything less than a direct attack upon the bleeding vessels is usually inadequate rather extensive and hazardous procedures, such as partial gastrectomy or duodenectomy, will be indicated since the vessel will often be on the posterior wall perforating onto the pancreas with much scarring present. Transfusions are of course most useful during such treatment and may be given by multiple portals. Six interesting case reports are included.

J. Duffy Hancock, Louisville.

SMITH, RICHARD M.

Chronic Idiopathic Ulcerative Colitis in Children. New England Jour. of Med., 217, No. 14, 541-546, Sept., 1937.

A brief differential diagnosis of melena is given. The clinical course of chronic ulcerative colitis is described, progression of the disease with remissions occurring, associated with marked weight loss and anemia. He recognizes an insidious and an acute onset and reports an illustrative case of each.

An infectious origin is considered more likely though the diplostreptococcus described by Bargen is considered unproved.

Medical treatment may be classified under four headings:

1. Directed at the colon, sedatives as opium and bismuth, low residue diet, serum and vaccine.
2. Maintenance of adequate nutrition, high caloric diet with abundant vitamins, replacement of lost minerals.
3. Combatting anemia, transfusions, iron if borne.
4. Symptomatic, sedatives for pain.

Surgery is indicated because of the danger of perforation or of polyposis followed by malignancy. The time for surgery is when fibrosis begins as shown by the loss of haustrations, narrowing of the lumen. Ileostomies are considered permanent in adults, in children it may be possible to restore normal continuity in two or three years.

The end results in twenty-seven cases are tabulated.

Medical treatment, nine cases. Five well, two still acute. Two deaths, one of perforation, one of carcinoma.

Surgical treatment, eighteen cases. Nine alive, five closed. Nine deaths, two of perforation after ileostomy, one of perforation after colectomy, two of volvulus after ileostomy, one operative death with ileostomy, one acute ileitis after ileostomy, one peritonitis after closure, one tracheobronchitis two months after surgery.

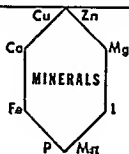
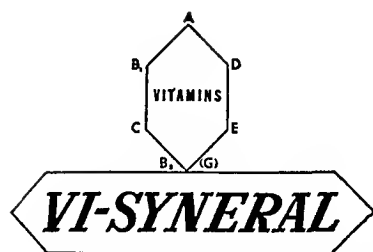
The cases receiving medical treatment were generally milder. It is concluded that surgery, meaning ileostomy, offers the most in these cases and that it should not be delayed too long.

COMMENT

This paper does not emphasize the surgical risk that the figures given show. Too many of the deaths are the result of surgery, experience which has been duplicated elsewhere in this disease. Surgery did not prevent perforation in two cases, and the mortality of 50 per cent in the surgical group is not encouraging.

K. W. Benson.

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1. Report of League of Nations Health Comm., Dec. 6, 1935

2. Eddy, Walter E. (Special research report on Vi-Syneral).

3. Privitera, A. T., Arch. of Ped., April, 1938.

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PROUTY, JAMES V.

Regional Enteritis. Jour. Iowa State Med. Soc., 27:379-382, Aug., 1938.

Regional enteritis may be encountered in an acute or chronic form. It may involve one or more areas in the jejunum, ileum, or colon. The etiology is unknown. The pathology consists of an acute or chronic nonspecific inflammatory process. The symptoms depend upon the severity, duration, extent and location of the lesions. They may simulate appendicitis, ulcerative colitis, obstruction, or malignancy. The preoperative diagnosis depends largely upon proper roentgen examination. The treatment is essentially surgical.

Hanes M. Fowler, Fort Wayne.

RAO, M. NARASIMHA.

Histidine and Peptic Ulcer. Jour. Indian Med. Assoc., 7:518, June, 1938.

In a series of sixteen cases of peptic ulcer treated with histidine 3 cases were classified as cured. In one case there was only symptomatic relief. Ten of the cases showed no improvement or otherwise. Two of the cases got definitely worse. Estimations of progress were based upon symptomatic, radiological and biochemical evidences, and the cases were "followed up" for one year after the treatment which consisted of an average of 21 to 25 daily intramuscular injections of 5 cc. of 4% histidine monohydrochloride.

Hanes M. Fowler, Fort Wayne.

VOEGLIN, WALTER L.

Some Novel Manifestations of Ascariasis. Northwest Med., 37:182-183, June, 1938.

This is a report of an unusual case of ascariasis in which the parasites migrated into the common bile duct, and up through the stomach into the esophagus and pharynx at times. The symptoms produced were upper right quadrant pain, polyphagia, pain in the chest, and foreign body sensation in the esophagus. The patient extracted one worm from her pharynx with her fingers. Caprakol and hexylresorcinol caused the evacuation of seven worms and disappearance of all symptoms.

Hanes M. Fowler, Fort Wayne.

At the meeting of the Central Society for Clinical Research (reported in the J. A. M. A., 110:687, 1938) Rynearson reported having been able to get rid of individual hypersensitivity to protamine zinc insulin either by giving histaminase by mouth or histamine injections.

W. C. Alvarez, Rochester.

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MCCULLOUGH, NORMAN B.

Vitamin C and Resistance of the Guinea Pig to Infection with Bacterium Necrophorum. Jour. of Infectious Diseases, 91, 34-53, July-Aug., 1938.

There is much contradiction in previous work relating Vitamin C to infection. Diets may have been deficient in other essentials. Crude sources of Vitamin C have been used. Virulent organisms have been used making survival period the only criterion.

It has been demonstrated that chronic C deficiency shortens the survival of the guinea pig with tuberculosis. Excess of the vitamin doesn't alter the course of the disease. Injections of streptococcus toxin will produce rheumatic fever like lesions in the scorbutic guinea pig. C reserves are lowered in febrile disease as might be expected from the increased metabolism. Vitamin C has antitoxic effect in diphtheria, and some protective action against anaphylactic shock.

Several strains of bacterium necrophorum (bacterium funduliforme) were isolated from cases of chronic ulcerative colitis. It is not assumed that these are the causative organisms. Fifty guinea pigs that had been kept seven days on a C deficient diet were inoculated in the abdominal wall, thirty-one developed low grade local infections not affecting body weight. Fifty controls on an adequate diet were unaffected by the inoculations.

Forty-five guinea pigs were just kept from having acute scurvy by minimal doses of Vitamin C. None developed infection following inoculation with bacterium necrophorum.

Bovine strains of bacterium necrophorum, slightly more pathogenic to the guinea pigs, were injected into normal and deficient guinea pigs. In the deficient animals the lesions were more severe and did now show a tendency to heal spontaneously. After seven days the deficient animals were given crystalline Vitamin C, those that were not moribund recovered rapidly from the scurvy and the infection.

It is concluded that a very severe grade of scurvy is necessary to reduce the resistance of the guinea pig to these organisms. In clinical practice Vitamin C deficiency must be marked to account for a low resistance to infection.

K. W. Benson.

BROOKS, CLARK D., CLINTON, WM. R. AND ASHLEY, L. BYRON.

Primary Carcinoma of the Jejunum. Jour. Mich. State Med. Soc., 37:795-797, Sept., 1938.

Primary carcinoma of the jejunum is not only an infrequent lesion, but an interesting one as well, because of the difficulty in making an early diagnosis, the irregularity of the symptoms, and the unusual response to surgical treatment. The incidence is only 0.15 per cent of all gastrointestinal carcinomas, according to the most recent survey by Mayo and Nettrour.

Two cases are reported with descriptions of the symptoms, operation, and post-operative progress. Both cases made uneventful recoveries after operation, and are in good health twenty-eight and eighteen months, respectively, after operation.

Hanes M. Fowler, Fort Wayne.

WINFIELD, JAMES M.

The Use of Dried Bile as a Therapeutic Agent. Jour. Mich. State Med. Soc., 37:798-802, Sept., 1938.

The symptoms associated with lack of bile in the gastrointestinal tract are lack of strength, anorexia, distention, constipation and malaise. The gastric and intestinal motility and tone are decreased, the stools become clay



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colored and greasy and loss of weight is quite common. A preparation of dried bile is described which was found to be effective in relieving the symptoms commonly associated with lack of bile in the intestine, particularly anorexia. The dried bile also had a slightly laxative effect. It also forms a simple means of supplying additional bile so necessary for the absorption of Vitamin K in jaundiced patients.

Hanes M. Fowler, Fort Wayne.

BARNES, J. PEYTON.

Appendectomy Mortality.. Texas State Jour. Med., 34:360-363, Sept., 1938.

Every year 17,000 persons die from appendicitis peritonitis. Records of 228,598 appendectomies have been collected with a mortality rate of 1.09 per cent. Operation for non-ruptured appendix has a mortality of 0.8 per cent, practically the same as that for simple hernia repair. Operation for ruptured appendix has a mortality rate of 18.3 per cent, based on 13,965 cases.

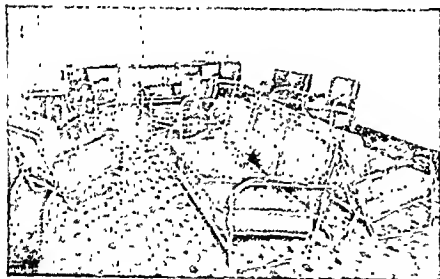
The author feels that a prophylactic appendectomy is indicated if an individual has ever had a distinct attack of appendicitis, or if he presents symptoms which create a doubt as to the innocence of the appendix. The above figures, gathered from many hospitals and made by thousands of different doctors, prove definitely that the disease is more dangerous than the operation, even in the hands of the average operator.

Hanes M. Fowler, Fort Wayne.

BARGEN, J. ARNOLD, JACKMAN, RAYMOND J. AND KERR, JACK G.

Studies on the Life Histories of Patients with Chronic

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Ulcerative Colitis with Some Suggestions for Treatment. Annals of Internal Med., 12:339-352, Sept., 1938.

A chiefly statistical study was made of the records of 871 patients who had thrombo-ulcerative colitis and who have been followed from 7 to 14 years after the first observation.

Predisposing factors and factors affecting relapses of the disease are chiefly the following: Upper respiratory infection, disease of childhood, dietary indiscretion, physical and mental fatigue, rectal or abdominal surgery, trauma, drastic catharsis, foci of infection with sepsis, exposure, dysentery epidemics, and pregnancy.

This disease may begin in an insidious manner. Again, it may come on suddenly, as a violent diarrhea without toxic symptoms, or it may start in a fulminating fashion, associated with marked toxemia, fever and all the concomitants of a severe septic process.

On the basis of its course, the disease can be readily divided into the following types: (1) mild throughout, (2) intermittent with declining severity, (3) septic with complete recovery, (4) constant without remission, (5) slowly progressive without remission, (6) intermittent with progressive severity, (7) insidious onset with slow progression, changing to a fulminating condition and ending fatally, and (8) fulminating throughout, ending fatally.

The major complications and sequelae of thrombo-ulcerative colitis include polyposis, stricture, perianal abscess—fistula, arthritis, erythema nodosum, pyoderma gangrenosa perforation, liver abscess, carcinoma phlebitis, iritis, deafness, splenomegaly, nephritis, psychosis, massive hemorrhage, endocarditis and kidney stones.

Surgical intervention in this disease should be limited to complications and sequelae. An individual afflicted with thrombo-ulcerative colitis presents a poor surgical risk if a surgical attempt must be made to relieve another intercurrent abdominal pathologic condition.

The end results of this infection may be devastating but it may also end in complete relief of all symptoms and signs of intestinal pathologic change. This happy result occurs frequently enough to make it urgent that a well-ordered regimen be followed without deviation by these patients for months and years.

Hanes M. Fowler, Fort Wayne.

CONNELLY, RICHARD CAMPBELL.

Colloidal Aluminum Hydroxide Therapy in Upper Gastro-Intestinal Lesions. Jour. Mich. State Med. Soc., 37:706-711, Aug., 1938.

Colloidal aluminum hydroxide serves as a buffer of hydrochloric acid and so reduces the irritating action of the gastric secretion on the injured mucosa of the stomach and duodenum. It may also inhibit digestion of a blood clot over a bleeding ulcer. The substance is fairly palatable and does not ordinarily produce nausea. Its use even over as long a period as one year seems to produce no harmful action on blood cytology or chemistry.

Colloidal aluminum hydroxide proved to be an antacid of considerable value in the treatment of twenty peptic ulcers, and it seems to possess an advantage over the alkali treatment of ulcer. The aluminum hydroxide has no laxative action, so provision must be made for this need in certain cases.

Hanes M. Fowler, Fort Wayne.



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DRAGSTEDT, CARL A.

Some Pharmacological Considerations of Intestinal Obstruction. Illinois Med. Jour., 37:313-315, Oct., 1938.

Experimental evidence indicates that there can occur a transperitoneal absorption of toxic material from a strangulated bowel, and there is also evidence of the mesenteric absorption of toxic material under certain circumstances. In addition to the toxemia, the other factors suggested as operating in cases of obstruction are dehydration and loss of electrolytes from the blood, interference with the circulation, and some unexplained nervous factors.

The mechanical interference with circulation caused by severe distension is a quite important factor. The present interpretation of the beneficial effect of morphine in cases of ileus is that it is due to the indirect effect of morphine improving the circulation through the bowel by promoting tone and motility in the intestine.

Hanes M. Fowler, Fort Wayne.

GREEN, JOHN A.

(Ileus) Intestinal Obstruction. Illinois Med. Jour., 37:315-319, Oct., 1938.

Ileus is a symptom-complex characterized by pain, vomiting, tympanites and obstipation. According to Dean Lewis' classification, ileus may be divided into: mechanical ileus, as seen in carcinoma, bands, volvulus, intussusception, foreign bodies, etc.; strangulation ileus in which vessels are involved as in embolism or thrombosis; adynamic ileus in which the musculature of the bowel wall is paralyzed as in peritonitis and other acute abdominal conditions; dynamic ileus in which the musculature of the bowel wall is contracted, as in lead poisoning, and diseases of the central nervous system.

Intestinal obstruction continues to be one of the most deadly of all intestinal conditions and causes about the same mortality that it did two if not three decades ago. The mortality rate in ileus as given by different reports still varies between 40 and 70 per cent. The greatest cause of this high death rate is delay in treatment.

Ileus is a very frequent, if not the most common cause of postoperative abdominal complications. This deplorable situation can only be improved by becoming ileus conscious, which will result in earlier diagnosis, earlier recognition of the types and earlier institution of treatment. Until this takes place, and the patient, by means of popular medical education is also made to realize the danger of delay, no better end results may be expected.

Hanes M. Fowler, Fort Wayne.

ROSENBLUM, PHILIP.

Intussusception. Illinois Med. Jour., 74:309-313, Oct., 1938.

Intussusception is essentially a pediatric disease, 75 per cent of the cases occurring in infants under one year of age. The incidence in males over females is practically 2 to 1.

The most common symptoms in the acute variety are sudden onset in infants usually under one year, intermittent colicky pain, vomiting a palpable mass and blood in the stool. It is sometimes necessary to give an analgesic or anesthetic in order that the mass might be felt. Roentgen ray examination is very helpful especially in the subacute and chronic types.

The following conditions should be considered in the differential diagnosis, acute appendicitis, bleeding Meckel's diverticulum, prolapse of the rectum, dysentery, Henoch's purpura, tumors of the rectum, thrombosis of the splenic vein, and foreign bodies in the rectum.

The earlier the diagnosis the better the prognosis, and the importance of postoperative care, such as supplying fluids, is most essential.

Hanes M. Fowler, Fort Wayne.

COLEMAN, G. H. AND CAPPS, J. A.

Diverticulitis of the Colon. A preliminary report of a study of its potential role as a focus of infection in systemic disease. Ach. Path., 26-1, 207, July, 1938.

The authors give a preliminary report of 11 cases of diverticulitis associated with rheumatoid arthritis as a major complication in which detailed stool cultures gave predominant growths of *Str. haemolyticus* in 9 of the 11 cases. As a control group for comparison 1600 routine stool cultures from persons without evident diverticulae of the colon and arthritis gave 180 which were positive for *Str. haemolyticus* or 11 per cent, as opposed to 8 per cent. Furthermore with treatment of the patients which resulted in sharp reduction of the number of colonies present in the stools there was a parallel improvement noted in the condition of the arthritis.

N. W. Jones, Portland.

Colcher (Radiology, 29:615-621, 1937) suggested a number of improvements in the method of bringing out the mucosal markings of the stomach. The trick is to get the right amount of barium mixture and then to get the patient in the right position so that the various folds become visible. With this technic, popularized by Berg and others, some ulcers, previously invisible, can be discovered.

W. C. Alvarez, Rochester.



Red Cross Methods in Epidemic Control

DURING flood relief operations in the Mississippi Valley of 1937, Red Cross workers at a refugee camp in Northwestern Arkansas suddenly found themselves confronted with what gave promise of becoming an epidemic of cerebrospinal meningitis. The first case was reported February 5, two additional cases on February 7 and after that new cases were reported almost daily.

Local hospital facilities were crowded and the first 12 cases were cared for in a tent hospital. Subsequently a wooden barracks with three wards and a diet kitchen, of which a portion was screened off for records, supplies and scrubbing facilities were erected. To make a long story short, the last of 36 cases was admitted March 24, the hospital was closed April 3, and the remaining two convalescing patients transferred to the local hospital.

Contributing factors which were largely responsible for keeping the threatened serious epidemic within bounds included the following, according to Dr. William DeKleine, of the American Red Cross:

Daily inspection of the camp population; early diagnosis and treatment; repeated throat cultures of patients, carriers and contacts (326 in all); prompt isolation of quarantine and continuous follow-up care of all cases. National guardsmen prevented mingling of carriers and contacts with other people.

The epidemiological studies indicated that all cases, with but two exceptions, reported from one camp at Jonesboro, could be traced directly to the first patient. Most contacts occurred at camp, some in transit to the camp. Complete separation of carriers, contacts and patients until they can no longer transmit the disease, is highly important, according to the report. In Dr. DeKleine's opinion it is better to keep a few doubtful carriers in quarantine than to permit a single case to run at large. During the quarantine period treatment should be given.

Work of the Red Cross is dependent upon support from its individual members. Their dues finance its activities. The annual Roll Call for members for the coming year will begin Armistice Day and end Thanksgiving.



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The Gastric Absorption of Phenol Red in Humans*

By

ABRAHAM PENNER, M.D., FRANKLIN HOLLANDER, Ph.D.

and

MAX SALTZMAN, B.S.

NEW YORK, NEW YORK

A DILUTION indicator in gastric analysis is a substance used in the quantitative determination of the relative amounts of test-meal and secretion present in a sample of gastric contents recovered during the course of a test-meal series. It is essential that any substance used for this purpose must not disappear from the stomach except by loss through the pylorus. Such disappearance may occur through (1) absorption by the gastric mucosa, (2) adsorption on the surface of the mucosa, or (3) chemical change of the indicator by reaction with gastric contents. In the past, phenol red has been used by several investigators with the tacit assumption that the above condition has been met. (Gorham, 1923; Bulger et al, 1928; Wilhelmj et al, 1933).

Before proceeding in our own laboratory to use phenol red as a dilution indicator, we decided to investigate the validity of this assumption. In order to avoid complicated operative procedures which might tend to confuse the results by creating unphysiological conditions, it was decided to employ a substance which is already known not to be absorbed by the stomach as a standard of reference to be quantitated parallel with the phenol red. Such a substance was found in iron alum, $\text{Fe}_2(\text{NH}_4)_2(\text{SO}_4)_4$. The introduction into the stomach of a weakly acid solution of this salt and phenol red in known concentrations makes it possible to determine whether or not the dye is lost by any mechanism other than passage through the pylorus. Since the iron is not absorbed, failure of absorption of the phenol red should result in a constant ratio of iron to phenol red concentrations in all the specimens recovered in the test-meal series. If phenol red is absorbed, this ratio should increase progressively in any single series.

Evidence on the absorption of iron by the stomach has been confused by the use of surgical procedures, resulting in the creation of abnormal conditions in the stomach and introducing unknown and uncontrollable variables (Stalkenstein, 1927; Delhougne, 1931). However, since the time of Hari (1898) and Abderhalden (1900), the majority of investigators have reported that iron was not absorbed from the stomach. All these investigators allowed solutions of an iron salt to remain in contact with the non-operated gastric mucosa of various animals for varying intervals of time and then, sacrificing the animals, used histological methods to demonstrate the presence or absence of iron in the mucosa. The observations were uniformly negative. A critical review of the subject by Tartakowsky (1903) substantiated his own negative

results obtained by the same methods. An even more extensive critical review by Lintzel (1931) twenty-eight years later led to the same conclusion.

PROCEDURE

Our experimental subjects consisted of patients with unoperated gastro-intestinal tracts. In choosing our subjects we were especially careful to include a variety of gastric and systemic pathological conditions in order to obtain data of some general applicability. The individuals were preferably ones who were accustomed to swallow the stomach tube ordinarily used in obtaining gastric test-meal series. The tube was introduced into the fasting stomach; this viscus was emptied of such contents as were present and it was then washed with 100 ml. of the test-meal described below. This was followed by the introduction through the tube of varying amounts of the same test meal. Samples of gastric contents were then withdrawn periodically in the following manner: the entire contents of the stomach were removed, mixed thoroughly, and after 15 ml. had been separated for analysis, the remainder was returned to the stomach via the tube. This process was repeated at 15 or 30 minute intervals until the stomach was empty. A special effort was made to avoid trauma and bleeding, and if any blood was noted in a sample the entire series was discarded. The quantity of the test meal originally introduced varied from 150 ml. to 400 ml. depending upon the gastric capacity and tolerance of the subject.

COMPOSITION OF THE TEST MEAL

The test meal consisted of a solution of phenol red and $\text{Fe}_2(\text{NH}_4)_2(\text{SO}_4)_4$ made up in 0.01 N H_2SO_4 . Except for one experiment, the phenol red was used in two concentrations; namely, approximately 4 and 8 mg. per cent. The iron content was uniformly in the region of 0.04 N. The test-meal was acidified in order to avoid loss of iron by hydrolysis and the precipitation of basic salts in an acid gastric contents. The concentration of H_2SO_4 was kept at 0.01 N since it was found that gastric intolerance to the test-meal may result from higher concentrations. Inasmuch as the final results were to be expressed in terms of the ratio of the concentration of iron to the concentration of phenol red, in each of a series of samples of gastric contents, the components of the test-meal were measured out in close approximation to the above values and the ratios of the samples compared with the corresponding ratio for the test-meal, used in the same experiment.

DETERMINATION OF PHENOL RED

Phenol red was determined according to the method recently described by us. (Hollander, et al, 1937).

DETERMINATION OF IRON

A slight modification of the method of Fowweather (1926) was employed. 2 ml. of the sample of gastric

*From the Laboratories of the Mount Sinai Hospital, New York City. (This work was supported in part by a grant from the Friedsam Foundation).

contents were introduced into a Pyrex test tube (200 mm. x 25 mm.) which had been previously graduated to contain 50 ml. One ml. of 36 N H_2SO_4 was added and the mixture was heated to boiling until the first dense white fumes of H_2SO_4 appeared. The solution was blackened by carbonization of the organic matter present. After cooling for one minute, one ml. of Superoxol was added slowly along the side of the tube by means of a dropper. Violent bubbling and clearing of the solution resulted. When the bubbling had practically ceased the mixture was again heated to the first appearance of dense white fumes. If, at this point, further charring occurred, one ml. of Superoxol was again added in the same manner as before; this process was repeated as often as necessary to remove all organic matter. If, however, the solution took on merely a faint yellowish-brown or amber color it was allowed to cool, since it was found that this color disappeared on cooling and left a colorless solution. Special precautions were taken to stop heating at the first appearance of the dense white fumes of H_2SO_4 , because further heating usually resulted in the appearance of a finely dispersed white precipitate which did not readily dissolve on subsequent treatment and thus introduced an appreciable error in the method. The

solution was allowed to cool to room temperature and 5 ml. of distilled water were added. This was followed by the addition of 20 ml. of 0.5 N H_2SO_4 , 2 ml. of saturated $\text{K}_2\text{S}_2\text{O}_8$ and 5 ml. of 4 N KSCN , and then by dilution to the 50 ml. mark with 0.5 N H_2SO_4 . The tube was closed with a rubber stopper, thoroughly mixed by inversion, and the solution was then compared with a suitable standard in a colorimeter.

For this standard of reference, we used an approximately 0.04 N solution of $\text{Fe}_2(\text{NH}_4)_2(\text{SO}_4)_4$. It was not necessary to know its exact concentration because all the measured concentrations were calculated relative to that of iron in the test-meal itself. Two ml. of this solution were pipetted into one of the graduated Pyrex test tubes. To this were added 20 ml. of 1.5 N H_2SO_4 , 2 ml. of saturated $\text{K}_2\text{S}_2\text{O}_8$, and 6 ml. of 4 N KSCN ; this mixture was then made up to volume with 1.5 N H_2SO_4 in the usual way. The color of this reference solution was found, by comparison with freshly prepared solutions, to undergo no change for at least one hour after it was prepared.

All determinations were done in duplicate.

For the purpose of establishing the reliability of the method, we prepared a large series of solutions of $\text{Fe}_2(\text{NH}_4)_2(\text{SO}_4)_4$ of different concentrations and made up with a variety of specimens of human gastric contents as diluent. These specimens differed widely in regard to the amounts of acid, mucus, and bile which they contained. The iron concentrations were determined in these solutions and compared with their calculated values. The results are presented in Table I. The last column of this table contains the percentage error in each determination reckoned as the difference between the calculated and observed values, divided by the calculated value itself. Of the 25 specimens listed, only 3 yielded errors of greater than ± 2 per cent, whereas 11 of the observed values were in exact agreement with the calculated. Better than this, however, as a measure of the precision of the method, is the probable error of a single determination as calculated from all 25 individual errors. The value of this statistical characteristic was found to be ± 0.62 per cent of the actual concentration, which betokens a precision entirely adequate for the present purpose.

In order to investigate the applicability of Beer's Law in this procedure, iron determinations were carried out on a series of known solutions in concentrations varying from 156 mN to 0.78 mN. The standard of reference was maintained uniformly at a concentration of 39 mN. Nevertheless the observed values were invariably in agreement with those calculated according to the straight line relationship of Beer's Law—within the limits of error of the method.

SUBJECTS

Case 1. (B. B., Series Jp5) A 42 year old male, admitted to the Medical Service of Doctor George Baehr, with a 12 year history of proven duodenal ulcer which, in the 6 months preceding admission, had led to an incomplete pyloric obstruction. There was a 12 hour "gastric retention" of 40 ounces at the time the gastric analysis was done. He subsequently had a subtotal gastric resection and the resected specimen revealed a marked "gastritis" as well as a stenosing duodenal ulcer.

Case 2. (A. C., Series Jp7) A 40 year old Puerto-Rican male, admitted with an icterus due to a cholangitis of unknown etiology to the Medical Service of Doctor George Baehr. Rehfuess test meal showed a normal acidity curve. A gastro-intestinal X-ray series showed no ab-

TABLE I

Reliability of the iron method as shown by a series of determinations on solutions of known concentration

Specimen No.	Bile	Concentration of Iron		Error*	
		Calculated	Observed	mN	%
1	0	39.0	33.7	-0.3	0.8
2	0	39.0	39.0	0.0	0.0
3	0	7.8	7.2	-0.6	8.0
4	0	7.8	7.7	-0.1	1.3
5	0	39.0	39.5	+0.5	1.3
6	0	7.8	7.8	0.0	0.0
7	0	7.8	7.8	0.0	0.0
8	tr.	3.9	3.3	-0.1	2.6
9	tr.	3.9	3.8	-0.1	2.6
10	tr.	0.78	0.78	0.0	0.0
11	tr.	0.78	0.78	0.0	0.0
12	tr.	3.9	3.9	0.0	0.0
13	tr.	3.9	3.9	0.0	0.0
14	tr.	0.78	0.78	0.0	0.0
15	tr.	0.78	0.78	0.0	0.0
16	+++	39.0	38.4	-0.6	1.6
17	+++	39.0	38.7	-0.3	0.8
18	+++	39.0	38.9	-0.1	0.3
19	+++	39.0	38.9	-0.1	0.3
20	+++	15.6	15.7	+0.1	0.6
21	+++	15.6	15.5	+0.1	0.6
22	+++	15.6	15.6	0.0	0.0
23	+++	15.6	15.6	0.0	0.0
24	++	73.0	77.8	-0.2	0.3
25	++	73.0	77.8	-0.2	0.3

*The error was calculated as the difference between observed and calculated values. Percentage error was obtained by dividing the error expressed as mN by the actual concentration.

TABLE II
Constancy of the iron-phenol red concentration ratios

Series No.	Specimen No.	Time Hours	PR conc. mg. %	Fe conc. $N \times 10^{-2}$	Fe conc. PR conc.	Residuals ²	P. E. ³
(1)	(2)	(3)	(4)	(5)	(5)	(7)	(8)
Jp5	2	0	0.37	0.805	0.926	0.017	0.8%
	3	$\frac{1}{4}$	0.91	0.855	0.910	0.031	
	4	$\frac{1}{2}$	0.82	0.733	0.804	0.015	
	5	$\frac{3}{4}$	0.63	0.555	0.897	0.012	
	7	$1\frac{1}{4}$	0.23	0.248	0.885	0.023	
				Averages	0.909	0.020	
Jp7	T. M. ¹	0	4.42	3.80	0.850	0.005	1.5%
	1	$\frac{1}{4}$	3.88	3.12	0.804	0.051	
	2	$\frac{1}{2}$	3.23	2.78	0.861	0.005	
	3	$\frac{3}{4}$	2.50	2.24	0.896	0.041	
				Averages	0.855	0.025	
Jp8	T. M.	0	4.42	3.89	0.880	0.015	0.9%
	1	$\frac{1}{2}$	3.54	3.22	0.910	0.015	
	2	$\frac{3}{4}$	2.83	2.50	0.919	0.024	
	3	1	2.38	2.07	0.870	0.025	
				Averages	0.895	0.020	
Jp9	T. M.	0	3.95	3.90	0.985	0.004	0.1%
	1	$\frac{1}{4}$	1.88	1.86	0.989	0.000	
	2	$\frac{1}{2}$	2.89	2.85	0.990	0.001	
	3	1	2.28	2.26	0.991	0.002	
	4	$1\frac{1}{4}$	2.23	2.25	0.987	0.002	
	5	$1\frac{3}{4}$	1.93	1.97	0.995	0.005	
	6	$2\frac{1}{4}$	1.74	1.72	0.989	0.000	
	7	$2\frac{3}{4}$	1.67	1.55	0.988	0.001	
				Averages	0.989	0.002	
Jp10	T. M.	0	4.15	3.90	0.940	0.006	0.9%
	1	$\frac{1}{2}$	3.16	3.07	0.971	0.025	
	2	1	2.88	2.67	0.927	0.019	
				Averages	0.946	0.017	
Jp11	T. M.	0	4.15	3.90	0.940	0.042	0.9%
	1	$\frac{1}{2}$	3.38	3.32	0.982	0.000	
	2	1	2.83	2.82	0.995	0.014	
	3	$1\frac{1}{2}$	2.33	2.42	1.039	0.057	
	4	2	1.69	1.53	0.964	0.018	
	5	$2\frac{1}{2}$	1.10	1.07	0.973	0.000	
Jp12				Averages	0.982	0.023	0.4%
	T. M.	0	7.21	3.90	0.541	0.007	
	1	$\frac{1}{2}$	4.88	2.57	0.527	0.007	
	2	$1\frac{1}{4}$	3.51	1.85	0.531	0.003	
	3	$2\frac{1}{2}$	1.48	0.79	0.539	0.005	
Jp13				Averages	0.534	0.005	0.4%
	T. M.	0	7.02	3.90	0.556	0.008	
	1	1	6.25	3.53	0.555	0.001	
	2	$1\frac{1}{2}$	4.91	2.74	0.558	0.005	
	3	2	4.37	2.52	0.577	0.013	
	4	$2\frac{1}{2}$	3.40	1.94	0.571	0.007	
Jp14				Averages	0.554	0.008	0.2%
	T. M.	0	7.77	4.15	0.535	0.000	
	1	$\frac{1}{2}$	5.45	3.43	0.532	0.003	
	2	1	5.15	3.31	0.538	0.003	
				Averages	0.535	0.002	0.2%

(1) T.M. = Test meal.

(2) The residual is the difference between the corresponding value of the ratio and its mean value.

(3) P.E. = The probable error of the mean ratio. It is calculated from the formula $P.E. = 0.6745 \sqrt{\frac{\sum d^2}{n(n-1)}}$, where $\sum d^2$ equals the sum of the squares of the residuals, and n equals the number of specimens. The values given here are expressed as per cent of the mean value.

normalities. The test was done after the subsidence of the acute phase of the disease, but with the patient still showing a slight icterus.

Case 3. (L. B., Series Jp8) A 32 year old male, admitted to the Medical Service of Doctor George Baehr with a short history of vague abdominal pain and post-prandial distress. Rehfuß test meal showed normal free and total acidity curves, and a gastro-intestinal X-ray series was negative. Psychiatric examination supported the clinical impression of a "functional" basis of the symptoms.

Case 4. (L. H., Series Jp9) A 57 year old male with a long history of constipation, flatulence, and vertigo for which he had been observed in the gastro-intestinal clinic. His hemoglobin was 96 per cent Sahli with a red blood count of 5,600,000. A Rehfuß test meal series and a histamine test demonstrated a true achlorhydria; there was also a failure to excrete neutral red. A gastro-intestinal X-ray series showed no abnormalities.

Case 5. (M. S., Series Jp10) A 71 year old male observed in the gastro-intestinal clinic with a short history of anorexia, epigastric pain and sour brash, the latter coming on two hours after meals. He presented a marked loss of weight and a severe secondary anemia. Stool guaiac was positive. Rehfuß test meal series and histamine test both showed no free acidity. A gastro-intestinal X-ray series showed a mass protruding into the cardia. This was considered indicative of a carcinoma of the stomach.

Case 6. (P. C., Series Jp11) A 45 year old white male, admitted to the Medical Service of Doctor George Baehr with a history of having had several tarry stools one year previously as well as five days before admission. His hemoglobin was 22 per cent Sahli on admission. After several weeks of hospitalization a gastro-intestinal series showed a duodenal deformity indicating a duodenal ulcer without obstruction. A Rehfuß test meal series at this time showed a free acidity of 56 units and a total acidity of 81 units. The iron-phenol red test meal was administered during the period of convalescence.

Case 7. (D. M., Series Jp12) A 22 year old Puerto Rican male, admitted to the Medical Service of Doctor B. S. Oppenheimer with an attack of severe right upper quadrant pain. A thorough diagnostic work-up failed to indicate its etiology and exploratory laparotomy revealed only some perihepatic adhesions. Gastro-intestinal and gall bladder X-ray series revealed no abnormalities. Free hydrochloric acid was present in the vomitus.

Case 8. (M. Z., Series Jp13) A 67 year old white male observed on the Medical Service of Doctor George Baehr. He presented a six year history of dyspnea, angina of effort, anorexia, loss of weight and strength. Examination revealed a cachectic individual with no significant findings aside from lenticular opacities, pallor and weakness. His hemoglobin was 54 per cent Sahli with a red blood count of 2,500,000 and a color index of 1.1. Sternal biopsy revealed a picture considered typical of pernicious anemia. Rehfuß test meal series revealed an achlorhydria which persisted after histamine injection. There was no excretion of neutral red. Gastro-intestinal X-ray series showed no abnormalities.

Case 9. (M. A., Series Jp14) A 52 year old male admitted to the Medical Service of Doctor B. S. Oppenheimer with an eight weeks history of diarrhea and post-prandial substernal burning. Examination revealed a mass in the left cervical region. His hemoglobin was 90 per cent Sahli. Stool guaiac was negative. Biopsy of the mass in the neck revealed a columnar cell carcinoma. A complete roentgenologic examination of the gastro-intestinal tract revealed no abnormalities. He gradually went downhill with progressive cachexia.

RESULTS

The results are presented in Table II. The time

interval (column 3) between introduction of the test meal and withdrawal of the last specimen in any one series varied from one to three hours, depending on the exigencies of the case. The ratio of iron concentration to phenol red concentration is given in column 6, which also includes the mean value of the ratio for each series. Column 7 contains the deviations from this mean; the probable error of the mean ratio is given in column 8 as per cent of this mean. Occasionally a specimen was lost before the analytical determinations were completed. Also, in three instances not shown in the table, the deviations were so very much greater than the probable error calculated with exclusion of this value, that the specimen was disregarded completely in the analysis of the data. The statistical criterion which determines whether or not an individual specimen may be dropped in this way is that its deviation shall be greater than 4.5 times the probable error when the latter is calculated for all the observations excepting the one in question. By gross inspection of the results it will be noted that the values of the ratio in any one series are reasonably constant. Furthermore, in only one of the nine series of determinations (Case 2, Series Jp7) does the probable error possess a value greater than 1 per cent whereas in four of the series the value is less than 0.5 per cent. From this it may be concluded that no phenol red was lost in the stomach, under the conditions which obtained in these studies, except by passage into the duodenum.

Since the evidence for the non-absorption of the iron salt is solely histological, it may be objected that this evidence is not entirely conclusive. However, the histological method used is so sensitive that it is capable of demonstrating the most minute traces of iron in the tissues; when applied to the small intestine it gives a beautiful demonstration of absorbed iron throughout the entire length of the gut. The amounts of iron demonstrable may be so small that their passage from the gastric contents into and through the mucosa would not be recognizable as a change in concentration in the iron content of the test meal when analyzed by the method we have used. Hence, for our purposes, we may conclude that there is no significant absorption of iron through the gastric mucosa.

It will be noted also, from the variety of clinical conditions present, that pathological change in the gastric mucosa or in adjacent organs does not significantly affect the constancy of the concentration ratios. Thus our observations include the following: (1) Normal gastric mucosa (Cases 3 and 7); (2) Gastric mucosa unable to secrete hydrochloric acid in the absence of pernicious anemia or gastric carcinoma, due to inability of the parietal cells to function (Case 4); (3) Gastric mucosa unable to secrete hydrochloric acid and to produce the intrinsic factor of Castle; i.e., achlorhydria associated with pernicious anemia (Case 8); (4) Gastric carcinoma in a stomach unable to secrete hydrochloric acid but able to produce the intrinsic factor (Case 5); (5) Gastric mucosa in cases of duodenal ulcer, with and without pyloric obstruction (Cases 1 and 6); (6) Gastric mucosa in the presence of hepatic disease, with and without jaundice (Cases 2 and 7); (7) Gastric mucosa in the presence of the cachexia of carcinoma (Case 9). It follows, therefore, that the phenol red is not lost (except by passage through the pylorus) from the human stomach, normal or pathological, when present in concentrations which

vary from 0.87 mg. per cent to 7.77 mg. per cent. It is to be emphasized that these procedures were done under conditions as nearly "physiological" as possible and without operative trauma which might interfere with the functional activity of the gastric mucosa.

SUMMARY AND CONCLUSIONS

By the use of a known non-absorbable reference standard (ferric ammonium sulphate) it has been demonstrated that the substance, phenol red, is not absorbed from the human stomach, whether the mucous membrane is normal or altered by a wide variety of pathological processes. Furthermore, it has been demonstrated that phenol red is not altered chemically by its contact with the gastric secretions

under the conditions indicated, and that it does not preferentially stain the mucous membrane to a significant degree. In view of this it is concluded that we are justified in using phenol red as a dilution indicator in gastric analysis in humans.

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A Modification of the Anson and Mirsky Hemoglobin Method for the Determination of Pepsin in Gastric Drainage

By

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IN 1932 Anson and Mirsky (1) described a method for the determination of peptic activity in which hemoglobin was used as the protein substrate. As stated in their original publication on the method, "hemoglobin was chosen because it is easily prepared in large quantities, because it can be stored in solution for a long time without change, because it is rapidly digested, and because the rate at which it is digested by a given pepsin solution does not vary from one hemoglobin preparation to another." These qualities are not shared in toto by any other protein which has been suggested as a substrate for the estimation of peptic activity. Other proteins are not sufficiently reproducible so that results obtained with one preparation can be compared accurately with those obtained with another (2).

The method as originally described, although well suited to the needs of the enzyme chemist possessed a number of limitations which interfered with its value in the physiological or clinical study of the peptic activity of gastric drainage. Therefore, although the principles of the method have not been modified, the procedure has been altered in a number of respects. The incubation period has been lengthened in order to increase the sensitivity to gastric samples of low activity. The concentration of the hemoglobin has been increased in order to widen the range of peptic activity over which the method can be employed without it being necessary to resort to dilution of the more active samples. In addition, the unit has been changed so that when the activity is expressed as units per 100 cc. of gastric juice the values are in whole numbers. Since a number of other alterations have been introduced, the modified method will be presented in detail.

The method is based on the following principles.

When hemoglobin is incubated with pepsin under standardized conditions the amount of hemoglobin digested is an index of the activity of the pepsin. The extent of the digestion of the hemoglobin is estimated by precipitating the undigested hemoglobin with trichloroacetic acid, filtering, and determining the concentration of substances in the filtrate which give a blue color with phenol reagent (3). The intensity of this color is proportional to the amount of digested hemoglobin. The blue color is read in a colorimeter against the blue color produced by treating a standard tyrosine solution with phenol reagent. Thus the concentration of all trichloroacetic acid soluble materials which give a blue color with phenol reagent (tyrosine, tryptophane, and cysteine) are expressed in terms of tyrosine. The reagents give a slight but significant color when the determination is carried out without the addition of pepsin, and the gastric juice contributes a small amount of material which gives a color with phenol reagent. It is therefore necessary to control each determination by assaying a heat-inactivated sample of the gastric juice under investigation. The tyrosine equivalent of the inactive sample is then subtracted from that of the active sample leaving the true value for the tyrosine produced by the peptic digestion of the hemoglobin.

One unit of pepsin has been defined as that quantity which, acting at optimum concentration on 5 cc. of a four per cent solution of hemoglobin at a temperature of 37° C., will liberate each minute a quantity of trichloroacetic acid soluble material equivalent to one mgm. of tyrosine. At the optimum concentration the maximum digestion per unit weight of enzyme occurs, and the extent of the digestion is proportional to the concentration of the enzyme. This requirement is observed only when the enzyme is acting in low concentrations. As the concentration is increased the ratio

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of digestion to enzyme concentration becomes progressively smaller. In order to obviate the need for assaying every unknown enzyme solution in a series of dilutions in order to determine the optimum concentration and thus the activity, a curve has been prepared in which the tyrosine produced by the digestion is plotted against the units of activity (*vide infra*).

Preparation of reagents: The hemoglobin solution is prepared as described by Anson and Mirsky (1).^{*} The concentration of the final solution is determined by the Kjeldahl method, the nitrogen content of hemoglobin being 17.7%. This solution is then diluted with distilled water so that the final concentration of hemoglobin is 10 per cent. The working substrate is made up as needed by diluting two parts of the 10 per cent hemoglobin with three parts of N/8 hydrochloric acid.

The tyrosine standard is made up to contain 0.15 mgm. per cc. Thrice crystallized tyrosine should be used. The solution should contain 0.5 per cent formaldehyde as a preservative, and should be stored in the ice box when not in use. The other reagents used are: 4% trichloroacetic acid; N/10 hydrochloric acid; 3.85 N. sodium hydroxide, and Phenol reagent (3).

METHOD

Two test tubes containing 5 cc. each of acid hemoglobin solution are placed in a constant temperature water bath set at 37° C. When the contents of the tubes has assumed the temperature of the bath (about 15 minutes) 1 cc. of the undiluted gastric drainage is added to one of the tubes (Ostwald pipette). To the other is added 1 cc. of a sample of the same gastric juice which has been inactivated by heating in a boiling water bath for 5 minutes. In each case the gastric juice is mixed with the hemoglobin immediately after the addition by means of a whirling motion. Exactly 15 minutes after the middle of the pipetting period the undigested hemoglobin is precipitated by the addition of 10 cc. of 4 per cent trichloroacetic acid from another test tube. Thorough mixing of the digestion mixture and trichloroacetic acid is achieved by pouring the contents back and forth between the two tubes. The material is then filtered and 3 cc. of each filtrate is transferred to an Erlenmeyer flask. To the filtrate from the sample incubated with inactivated gastric juice is added 1 cc. of the standard tyrosine solution and 19 cc. of distilled water. The 1 cc. of standard tyrosine solution is added merely to increase the subsequently developed blue color to a readable intensity. To the filtrate from the sample incubated with active gastric juice is added 20 cc. of distilled water. A series of 5 standards containing 0.15, 0.30, 0.45, 0.75 and 1.05 mgm. of tyrosine respectively is made up by adding the appropriate volume of the tyrosine standard to Erlenmeyer flasks containing 3 cc. of N/10 hydrochloric acid each. The volume of each of the standards is then made up to 23 cc. with distilled water. To each of the flasks, standards and unknown alike, is added 1 cc. of 3.85 N sodium hydroxide followed by 1 cc. of phenol reagent. After 15 minutes, during which time the blue color reaches maximum intensity, the unknown solutions are read against the standard solutions which they most closely approximate. The standard is set at 20 in the colorimeter.

In practice a large number of samples can conveni-

^{*}In order to be sure that the final hemoglobin solution is at least 10 per cent, it is advisable to employ slightly less than an equal quantity of water when taking the corpuscles i. e. four parts of water to 3 parts of corpuscular suspension.

ently be assayed at one time by adding the gastric samples to a series of tubes containing hemoglobin at 30 second intervals and then, 15 minutes from the time the first sample was added, inactivating in the same order and at the same intervals by the addition of the trichloroacetic acid. In this manner we have assayed 20 unknown samples without confusion.

The quantity of tyrosine produced by the digestion of the hemoglobin is calculated according to the following formula:

$$\left[\frac{20 \times Sa}{Ua} - \frac{(20 \times Sb - 0.15)}{Ub} \right] \times 16/3$$

in which: Sa equals the mgm. of tyrosine in the standard against which the active unknown was read,

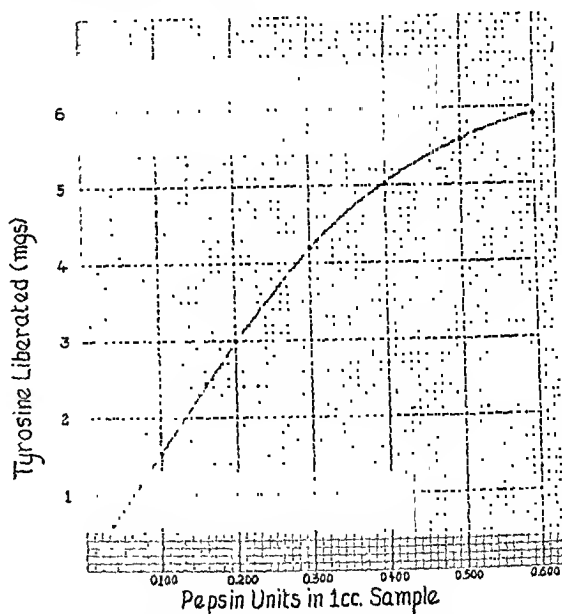
Sb equals the mgm. of tyrosine in the standard against which the inactive (boiled) unknown was read,

Ua equals the colorimeter reading of the active unknown, and

Ub equals the colorimeter reading of the inactive unknown.

The factor 16/3 is introduced to obtain the amount of tyrosine in the total quantity of digestion mixture.

This value is then converted into pepsin units per cc. of enzyme solution assayed by means of the curve (Fig. 1) mentioned above.



The curve was prepared in the following manner. The standard method was employed in determining the quantity of tyrosine liberated by a pepsin preparation of unknown potency acting in a wide range of concentrations. From these data a curve was prepared by plotting the tyrosine liberated against the quantity of enzyme. As would be expected, after a certain enzyme concentration had been reached, the digestion was carried to completion so that higher concentrations exerted no further effect. Conversely, in very low dilutions the extent of the digestion was so slight that it was not accurately measurable. Thus, it was possible to determine the range of enzyme concentration over which the method could be employed. The curve was then refined by determining the quantity of

tyrosine produced by the same enzyme preparation acting in concentrations within the narrowed range. From the part of the curve representing optimum enzyme concentration (i.e. the beginning of the curve where the quantity of tyrosine is proportional to the quantity of enzyme) the activity of the pepsin preparation was calculated. Then, having standardized the pepsin preparation in terms of units of peptic activity per unit weight, the values on the curve were expressed as units of activity rather than weight of enzyme preparation. Obviously, any pepsin preparation could have been employed in preparing the curve. In essence, the entire procedure is designed to standardize a given pepsin preparation and then to determine the quantity of tyrosine liberated by graded quantities when assayed according to the standard procedure. Since the value of the method depends to a large extent on the reproducibility of the hemoglobin, the curve herein presented should be universally applicable, providing, of course, that proper precautions are observed in the preparation of the hemoglobin solution.

The method becomes too insensitive to give accurate results when the activity of the sample analyzed is such that the quantity of tyrosine produced is greater than the maximum shown on the curve. Therefore it is necessary to appropriately dilute such specimens and repeat the determination. Conversely, when the quantity of tyrosine is so low that it cannot be read against the most dilute standard the determination should be repeated using a 30 minute rather than a 15 minute incubation period. Since doubling the incubation period is equivalent to doubling the quantity of enzyme, these tyrosine values can be converted to

pepsin units by means of the curve, by dividing the value obtained from the curve by two.

We believe that this is a method which after a little practice can be employed by the ordinary, trained laboratory technician and which will yield standard values, expressed as units, for the pepsin content of gastric drainage analyzed in different laboratories. This claim is made on the basis of the fact, originally observed by Anson and Mirsky (1), that the substrate hemoglobin is reproducible, a fact that we have confirmed and which after much experience have found not to be true for Mett's tubes, gelatin films, edestin, casein, etc. The next best method we have found is to determine the N. P. N. on the trichloroacetic filtrate after digesting a standard casein. This method is much more laborious and time consuming than the Anson and Mirsky method as adapted by us for assaying the concentration of pepsin in gastric juice.

COMMENTS

The sensitivity of the method is demonstrated by the results shown in Fig. 1 in which it is seen that the experimentally determined values yield a smooth curve with none of the points varying significantly from the general trend.

The preparation of the reagents, particularly the hemoglobin, is time consuming. However, the permanency and reproducibility of the final preparation, plus the simplicity and accuracy of the assay method, more than compensate for the time expended.

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Diabetes Mellitus and Peptic Ulcer

A Clinical Study of Nine Cases*

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THE coexistence of two diseases in an individual offers considerable material for intensive study and presents many problems for investigation. It is important to correlate the clinical and laboratory data, and to follow the course of each disease in order to determine whether any atypical features are present. Alterations in physiology produced by one disease may be significant factors in increasing or decreasing the patient's susceptibility toward development of the second disease. The clinician not infrequently finds that the usual therapy for one lesion must be modified because of complications introduced by the presence of the second disease.

In this study, the coexistence of peptic ulcer and diabetes mellitus has been investigated and is herewith reported. According to the reports of Landé (1), Dibold (2), Lesser (3), Holcomb (4) and Falta (5), cases of this type are encountered infrequently. In 1933, Dibold studied a series of 800 diabetic patients

and found peptic ulcer in only 7 of them. Landé's series of 2,100 diabetic patients included 22 with ulcer, whereas Falta found none with peptic ulcer in a group of 1,403 cases. During 1934 and 1935, there were 2,569 patients with diabetes admitted to Joslin's (6) clinic, among whom there were but 13 patients suffering from peptic ulcer.

The present study is based on all cases of diabetes mellitus and peptic ulcer admitted to the hospital from January, 1913, to August, 1936. During this period there were 130,500 hospital patients, of whom 3,525, or 2.7 per cent, had diabetes. Of this number of diabetic patients, only 9, or 0.25 per cent, had a coexisting peptic ulcer. There were 1,952 patients with proved peptic ulcer admitted during this time, constituting 1.49 per cent of all hospital admissions. Thus, the incidence of ulcer in the total of 130,500 patients was 1.49 per cent as compared with an incidence of 0.25 per cent in the 3,525 diabetic patients. Similarly, diabetes occurred in 2.7 per cent of the total number of hospital

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admissions, but in only 0.46 per cent of those patients with peptic ulcer. Table I. Portis and Jaffé (7) in necropsy studies on 339 cases of peptic ulcer found that diabetes was an associated pathologic condition

TABLE I

1913—1936	Total Hospital Admissions	130,500
1913—1936	Total Number of Diabetic Patients	3,625 — 2.7 per cent of total admissions.
1913—1936	Total Number of Ulcer and Diabetes	9 — 0.25 per cent of total diabetic patients.
1913—1936	Total Number of Peptic Ulcer Patients	1,952 — 1.49 per cent of total admissions.
1913—1936	Total Number of Ulcer and Diabetes	9 — 0.46 per cent of total peptic ulcer patients.

in but one case, constituting an incidence of approximately 0.3 per cent.

It would appear from the above statistics that people with diabetes mellitus, susceptible as they are to numerous medical and surgical complications, possess increased resistance to the formation of peptic ulcer. When our figures are added to those of the aforementioned authors, it is seen that there were but 51 cases of peptic ulcer in a total of 10,397 diabetic patients, or an incidence of 0.49 per cent. Table II.

In our group there were 6 females and 3 males. To evaluate these figures, it must be borne in mind that these two diseases have opposite predispositions for sex, namely, diabetes in females and peptic ulcers in males. Obviously, an indication of sex incidence can scarcely be obtained from such a small number of cases. In 6 patients the diabetes was known prior to the diagnosis of ulcer, while in the other 3 the ulcer apparently antedated the onset of the diabetes.

When the clinical picture of the average patient with peptic ulcer was compared with those having ulcer plus diabetes, several atypical features were noted. Patients with peptic ulcer usually have a definite association between food and pain, but in only 1 of our 9 patients did such a relationship exist. Relief of pain following intake of food is frequently found in the average case of ulcer, yet only 1 patient in our series gave such a history. Furthermore, but 2 of 9 patients told of having experienced relief of symptoms

TABLE II

	Number of Diabetic Patients	Number with Co-existing Ulcer	Incidence, Per Cent
Dibold	500	7	0.87
Landé	2,100	22	1.04
Falka	1,403	0	0.00
Joslin	2,550	13	0.50
Rathenberg & Teicher	3,625	9	0.25
TOTAL	10,397	51	0.49

following the intake of alkali medication. Although gastro-intestinal symptoms were the complaints for which all 9 patients sought hospital admission, their presenting histories and findings were not clearly defined. The diagnosis of peptic ulcer was made on admission in only 5 of the 9 cases. The remaining 4 patients entered the hospital with diagnoses of gall bladder disease in two, chronic constipation in one, and hepatic cirrhosis in the fourth patient.

The ulcers were located in the duodenum in 7 patients, on the lesser curvature of the stomach in one, and in the pylorus and duodenum in another.

Gastric analysis was performed in 7 of the 9 cases and hyperacidity was present in only 1 case. Five patients had normal acidity, 1 had subacidity, and the other had hyperacidity. It is interesting to note that the patient with hyperchlorhydria had no free hydrochloric acid in the fasting specimen.

The diabetic status of the patients was mild, and control was maintained without difficulty. This is evidenced by the fact that the complaints for which they sought hospital admission were related to stomach symptoms in all of the nine cases. Only three patients required daily insulin injections. Blood sugar levels were below 150 milligrams per 100 cc. in 4 cases, between 150 and 200 milligrams in 2, and above 200 milligrams in 3 cases. Complaints of polydipsia were elicited from 5 patients, polyuria was present in 4, and polyphagia was not reported in any of the 9 patients.

Six of the 9 patients were treated medically, and in this group greatest improvement was noted when the hospital diet was directed toward treatment of the ulcer rather than the diabetes. Three of these 6 left the hospital greatly improved on a Sippy diet regime. The other 3 medically treated patients were given diets for their diabetes, and left the hospital unimproved. Gastrojejunostomy was performed on 3 of the 9 patients. Of these, one made an uneventful recovery and was discharged free of complaints; one patient, aged 72 years, died of a cardiac collapse on the seventh post operative day; and the third, aged 65 years, died of uremia on the eighth post operative day. Table III.

COMMENT

Studies of gastric extractions after the usual Ewald meal in diabetic patients reveal a low acidity in a large proportion of cases. Wiechman (8) investigated 124 patients and found anacidity in 31, or 25 per cent of the total, subacidity in 18, or 15 per cent of the cases, normal acidity in 46, or 37 per cent of the series, and hyperacidity in 29, or 23 per cent of the total number. Thus, 40 per cent of his diabetic patients had a low gastric acidity, whereas in a group of normal people of corresponding age only 10 per cent would ordinarily show a hypochlorhydria or achlorhydria. Root (9) and Bowen and Aaron (10) also state that gastric acidity is decreased in diabetes. Dibold, Lesser and Lampé (11) point out that the degree of gastric acidity is affected by the level of the blood sugar and the use of insulin. Dibold stated that low acidity is usually found in the presence of high blood sugar, and conversely, high gastric acidity is brought about by hypoglycemia. He illustrated the effect of insulin in increasing gastric acidity and incidentally motility, by performing analyses of the stomach content of a diabetic patient over a twenty-four hour period. He found that the fasting specimen prior to administration of insulin contained

no free hydrochloric acid whereas, following the injection of insulin, free hydrochloric acid appeared and reached its highest level when the insulin effect was greatest. With the diminution of insulin effect on glycemia, there was a decline in the gastric acidity. Lampé emphasized the fact that in hypoglycemia, both gastric secretion and motility are increased. Thus, the diabetic patient, with diminished production of body insulin, can be made to secrete greater quantities of gastric hydrochloric acid by parenteral insulin injection. This relationship of blood sugar and insulin to the acid secreting cells of the stomach appears to be a definite one. At the present time however, it can not be stated whether gastric secretion is directly affected by the hormonal action of insulin, or by intermediate metabolic changes resulting from alteration of the blood sugar level.

The treatment of diabetes mellitus and peptic ulcer in the one individual presents many problems. High carbohydrate, low fat diabetic diets are unsatisfactory for ulcer patients and may cause activation of the gastric or duodenal lesions. It is likewise difficult to maintain an ulcer diet which will conform to diabetic requirements. We have found that results seem to be most satisfactory in those cases in which diet is directed toward treatment of the ulcer, and where the diabetic status is controlled by insulin injections whenever necessary. As previously noted, the three patients who were put on Sippy diets left the hospital improved, whereas the three patients who were receiving diabetic diets were not relieved of their gastric symptoms.

Fitz (12) and others agree that operative procedures on patients with both diabetes and peptic ulcer are undertaken with more than the usual risk. Surgery should be resorted to only after thorough medical treatment has proved ineffective and when there are indications that persistence of symptoms will endanger the life of the patient. Of the three patients in this series on whom surgical procedures were instituted,

intervention was necessitated by persistent bleeding in one case and pyloric stenosis in the other two.

A possible explanation for the infrequent occurrence of peptic ulcer in patients with diabetes mellitus may be found in studies of gastric acidity. In this series, only 1 patient in the group of 7 with records of gastric acidity gave evidence of hyperchlorhydria. In cases of proved peptic ulcer, this finding is most unusual! Furthermore, the hydrochloric acid in these seven cases of combined diabetes and ulcer averaged 53°, whereas in our cases of peptic ulcer without diabetes,* it averaged 68.1°. Root, in reporting achlorhydria in 30 to 40 per cent of diabetic patients, noted that the incidence of achlorhydria became greater with the longer duration of the diabetes as well as with the age of the patient. If, as many workers maintain, there is a definite relationship between gastric hyperacidity and formation of ulcer, then the lowered acid secretion in diabetic patients would seem to be one of the prime factors in decreasing their susceptibility to ulcer formation. However, some doubt is cast upon the lone role played by hyperchlorhydria in ulcer formation when one notes that 6 of our 9 patients developed ulcer despite the presence of diabetes for many years and despite the fact that they were found to have normal gastric acidity on hospital admission.

The possibility of failure to correctly diagnose gastro-intestinal complaints in a diabetic patient must be considered. The malnutrition and abdominal discomfort could be attributed to poor glycemic control and further diagnostic investigation be neglected. Holcomb and Dibold emphasize the point that persistent gastro-intestinal complaints in a well controlled diabetic patient requires careful exclusion of intrinsic gastric pathology as a possible causative factor. It is important to realize also that the etiology of glycosuria in a known ulcer patient must be investigated to exclude a pancreatitis as the source. Jankelson and Rudy

*Unpublished data, Jewish Hospital of Brooklyn.

TABLE III

Case Record No.	Age	Sex	Duration of Diabetes-Ulcer	Diabetic Symptoms			Blood Sugar Mgms. /100 cc.	Ulcer Relation of Pain to Food	Symptoms		Response to Dietary Treatment	Gastric Acid Total HCl	Course of Disease
				Polydipsia	Polyuria	Polyphagia			Pain Relieved by Food	Pain Relieved by Medicine			
162582	52 yrs.	Female	11 yrs. 3 yrs.	Yes	Yes	No	200	Yes	No	?	Poor	30°	Discharged unimproved.
169553	72 yrs.	Female	4 yrs. 2 wks.	No	No	No	350	Yes	No	Yes	Poor	65°	Discharged unimproved.
196507	48 yrs.	Female	9 yrs. 11 mos.	No	Yes	No	148	No	No	No	Poor	40°	Very slight change on discharge from hospital.
109742	58 yrs.	Male	6 yrs. 2 yrs.	No	No	No	140	No	No	No	Poor	47°	Operated. Discharged greatly improved.
140182	72 yrs.	Female	11 yrs. 6 wks.	Yes	Yes	No	130	No	No	?	Poor	?	Operated. Patient died.
120904	53 yrs.	Male	6 mos. 9 yrs.	Yes	Yes	?	155	Yes	Yes	Yes	Good	50°	Discharged improved on Sippy diet.
142108	46 yrs.	Female	On adm. 5 yrs.	Yes	No	No	250	No	No	No	Good	?	Discharged improved on modified Sippy diet.
105807	58 yrs.	Male	15 yrs. 6 mos.	Yes	No	No	140	Yes	No	?	Good	59°	Discharged improved on Sippy diet.
141212	65 yrs.	Female	5 yrs. 10 yrs.	No	No	No	330	No	No	No	Poor	80°	Operated. Died.

(13) reported three cases of peptic ulcer penetrating into the pancreas, with disappearance of the glycosuria post operatively. A type of glucose tolerance curve with a sharp rise in the first hour, followed by a return to normal within two and one-half hours, was found by van den Bergh and Von Henkelom (14) in cases of ulcer with pancreatic involvement. The simultaneous occurrence of duodenal ulcer with renal glycosuria in two brothers was reported by Meyer (15). It is apparent that when glycosuria is found in the presence of peptic ulcer, adequate medical investigation must be instituted to determine its etiology.

SUMMARY

1. In a group of 3,525 diabetic patients, peptic ulcer was present in 9 cases, constituting an incidence of 0.25 per cent. Of 130,500 total hospital admissions, 1,952 patients, or 1.49 per cent, had peptic ulcer. Both diabetes mellitus and peptic ulcer were present in 51 cases out of a group of 10,397 diabetic patients collected from reports in the literature.

2. Low gastric acidity is found in a large proportion of diabetic patients. To this fact, the infrequency of peptic ulcer in the presence of diabetes may be attributed. In 7 of our cases of peptic ulcer associated with diabetes, gastric acidity was normal in 5 patients, below normal in one, and above normal in another.

3. Ulcer symptomatology was atypical in a large proportion of the cases of coexisting diabetes mellitus and peptic ulcer. The diabetic status of these patients was mild and occasioned few symptoms.

4. Best therapeutic results were obtained in those cases of peptic ulcer and diabetes mellitus who were placed on a Sippy diet, with the diabetic status being controlled by insulin injections whenever necessary.

We are greatly indebted to Dr. Simon Rothenberg for his many helpful suggestions in the preparation of this paper.

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ABSTRACTS OF CASE RECORDS

Case No. 162582, a 52 year old female, with known diabetes for past 11 years. During this period, treatment had been dietary with occasional injections of insulin. Mild polydipsia and polyuria was present. For past three years, patient noted heaviness and fullness in epigastrium $\frac{1}{2}$ to 1 hour after meals. Eighteen pounds in weight had been lost in the nine months prior to hospitalization. Blood sugar was 200 milligrams per 100 cc. and the urine showed 2.5 per cent sugar. Gastric analysis showed free hydrochloric acid of 15 degrees and total acid of 30 degrees. X-ray examination demonstrated a constant deformity of the duodenal bulb. The patient was placed on a diet containing 150 grams of Carbohydrate, 60 grams of Protein, and 50 grams of Fat, with insulin Units 10 three times daily. Diabetic status was controlled, but no marked change in subjective symptoms followed. The patient be-

came very uncooperative and was discharged from the hospital unimproved.

Case No. 169853, a 72 year old female, with known diabetes for past 4 years, which had been treated by dietary measures only. For 2 weeks prior to hospital admission she suffered from a burning and soreness in epigastrium which came on 1 to 2 hours after eating and was not relieved by alkali medication. Blood sugar was 350 milligrams per 100 cc. and urine contained 1.6 per cent sugar. The highest readings on gastric analysis were 25 degrees for free hydrochloric acid and 65 degrees for total acid. X-rays demonstrated a large ulcer on the lesser curvature of the stomach with no gastric retention at 6 hours. Patient was placed on a diet containing Carbohydrate 150 grams, Protein 60 grams, and Fat 50 grams, and was given Insulin Units 5 three times daily. The diabetes was controlled on this regime but gastric symptoms persisted. Two days before discharge from hospital, Sippy diet and powders were given; on this course the patient began to experience some relief of symptoms.

Case No. 196807, a 48 year old female with known diabetes for 9 years. No insulin had ever been taken. Mild occasional pruritis vulvae and polyuria had occurred. For the past year, patient had noted a bitter taste in mouth, and on the day before admission had noted a tarry stool. Blood sugar was 148 milligrams per 100 cc. and urine showed 0.15 per cent sugar. Glucose tolerance test showed a typical diabetic curve. Fasting gastric specimen contained free hydrochloric acid, 12 degrees, and total acid, 36 degrees. Twenty-four degrees of free hydrochloric acid and 40 degrees of total acid were found in subsequent samples. An irregular duodenal cap was shown on X-ray. The patient was put on a diet of 160 grams of carbohydrate, 60 grams of Protein and 60 grams of Fat. During hospital stay, symptoms were not relieved.

Case No. 109742, a 58 year old male, with a 24 year history of alcoholism. Diabetes was known to have been present for past 4 years and dietary regime had been advised. Upper abdominal pain, nausea and belching, coming on 2 to 3 hours after meals, had been experienced for 4 months prior to hospital admission. Loss of 18 pounds in weight during this period. Examination revealed a smooth liver enlarged to level of umbilicus. Blood sugar was 100 milligrams per 100 cc. and urine showed 0.9 per cent sugar. Glucose tolerance test showed typical diabetic curve. Gastric analysis contained 18 degrees free hydrochloric acid and 47 degrees total acid. X-ray showed deformed duodenal cap and marked 6 hours gastric retention. On a Sippy diet the patient improved and was discharged from the hospital. He returned 2 years later because of recurrence of pain and daily vomiting. At operation, a large duodenal ulcer was found and a gastroenterostomy was performed. Postoperative course was uneventful, diabetes was controlled without insulin, and the patient was discharged from hospital free of complaints on a Lanhartz diet.

Case No. 140182, a 72 year old female with a known diabetes past 11 years, which was controlled by diet, and occasioned only mild polyuria and polydipsia. Epigastric pain present for four weeks before hospitalization. On admission, there was slight epigastric tenderness. Blood sugar was 130 milligrams per 100 cc. and urine showed 0.8 per cent sugar. X-ray showed an irregular duodenal bulb. Stools contained blood. Moderate secondary anemia was present, for which a transfusion was given preoperatively. At operation, a callus ulcer involving the first and part of the second portion of the duodenum was found. Gastroenterostomy was performed. Patient died on 7th post operative day of cardiac collapse.

Case No. 120904, a 54 year old male who for past 9 years had suffered from attacks of boring epigastric pain, belching, and sour eructations occurring 3 to 4 hours after meals. Exacerbation of symptoms for 2 weeks prior to

admission and appearance of tarry stools. Patient was found to have diabetes 6 months previous to hospital admission, which was controlled by diet alone. Mild polyuria and polydipsia was noted. Blood sugar was 150 milligrams per 100 cc. and urine showed 0.1 per cent sugar. Gastric analysis was performed and the highest degrees for free hydrochloric acid were 40, and for total acid, 50 degrees. X-ray studies revealed a deformed duodenal cap. Patient improved markedly on Sippy diet with alkaline powders, and diabetes was kept under control.

Case No. 142108, a 46 year old female with history of attacks of nausea and vomiting not associated with eating, occurring at irregular intervals during the past five years. Tarry stools on one occasion two years previously. Hematemesis three days prior to hospital admission, followed by recurrence of tarry stools. Blood sugar was found to be 334 milligrams per 100 cc. and urine contained 2 per cent sugar. Hemoglobin was 45 per cent with 2,180,000 Red Blood Cells per cm. A transfusion of 500 cc. of whole blood was given and the patient was placed on a Sippy diet. Response to treatment was good and the diabetes was controlled without insulin. X-ray examination revealed an irregular duodenal cap. Patient was discharged from the hospital on a Sippy diet much improved.

Case No. 105807, a 58 year old male, with known diabetes past 15 years. Epigastric pain radiating to back, belching, frequent vomiting, usually occurring 2 to 3 hours after meals, had been present for past 6 months. Sippy diet and daily doses of insulin had resulted in moderate relief of symptoms until four weeks before hospitalization when he experienced daily attacks of pain. On admission, the state of nutrition was poor. Moderate tenderness was elicited in right upper quadrant of abdomen. Blood sugar

was 176 milligrams per 100 cc. and urine contained 3 per cent sugar and 4 plus acetone. Analysis of vomitus revealed 36 degrees of free hydrochloric acid and 59 degrees of total acid. X-ray examination showed an irregular duodenal bulb and slight 6 hour gastric retention. Diabetes was controlled by three daily injections of 10 Units of insulin, and he showed rapid improvement of ulcer symptoms with Sippy diet and alkaline powders.

Case No. 141212, a 64 year old female, with known diabetes for the past ten years. Attacks of right upper quadrant abdominal pain that radiated to right shoulder, nausea and vomiting during past nine years. These episodes were unrelated to food ingestion. Exacerbation of symptoms during past four months caused patient to seek hospital admission. Physical examination revealed slight epigastric tenderness. Blood sugar was 208 milligrams per 100 cc. Gastric analysis showed a free hydrochloric acid of 48 degrees and a total acid of 80 degrees. A deformed duodenal bulb and marked 6 hour gastric retention was found on X-ray examination. Patient improved on a Sippy diet and was discharged from hospital. She returned nine months later because of recurrence of abdominal pain and vomiting. At operation, a stenosing duodenal ulcer pointing toward the pancreas was found. Gastroenterostomy was performed. For six days the post-operative course was fair and a mild glycosuria was controlled without insulin. However, for the next twenty days she vomited with increasing frequency and the blood sugar rose to 333 milligrams per 100 cc. Because of persistent vomiting, a laparotomy was performed and many adhesions in the region of the anastomosis were liberated. Post-operative reaction was poor, and the blood urea nitrogen, which had been normal, rose to 55.5 milligrams per 100 cc. The patient expired three days after the second operation.

End Results After Gall Bladder Operations With an Analysis of the Causes of Residual Symptoms*

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PATIENTS who have had biliary tract operations present themselves so frequently with abdominal complaints that they challenge the diagnostic and therapeutic resources of the physician. We undertook this study:

I. To ascertain what benefit was derived from biliary tract surgery insofar as preoperative symptoms were concerned.

II. To determine the causes of failure if biliary symptoms persisted.

III. To determine what conditions caused abdominal distress mimicking biliary symptoms before and after biliary tract surgery.

IV. To study the incidence of those diseases most commonly associated with biliary tract infections.

SELECTION OF MATERIAL

The 165 patients (Table I) reported by us represents all those we have encountered in the last eight years who were operated for biliary symptoms and

who could be adequately studied postoperatively. 199 operations were performed. Eighty-four operations (42%) were performed while under our care, the remainder were performed by others. All patients were personally studied by us. No written questionnaires were used. The patients were thus available for quizzing, physical, laboratory and X-ray examinations. A

TABLE I

199 gall bladder operations on 165 patients

Cholecystectomy for Calculous Cholecystitis	102
Cholecystectomy for Non-calculous Cholecystitis	34
Removal of stones from cystic duct	2
Common Duct Operations	11
Severance of Post-Operative adhesions	4
Exploratory Operations on Gall Bladder	12
	199

*From the North End Clinic, Detroit.

patient might appear for an unrelated complaint, as an acute upper respiratory tract infection, but if she had had a gall bladder operation, data were obtained relative to the type of operation, symptomatic relief, etc.

Thirty-one per cent of the patients were seen in

TABLE II
Follow-up period after 136 cholecystectomies

6 months to 1 year	6%
1 year to 5 years	36%
6 years to 10 years	20%
10 years or more	38%
Average follow-up period 7.5 years.	

clinic practice, the remainder in private practice. Eighty-two per cent of our patients were Jewish. There were no colored patients, although the incidence of colored patients admitted to our clinic is 26%.

RESULTS OF CHOLECYSTECTOMY

The average period of follow-up study was 7½ years. Thirty-eight per cent were followed ten years or more (Table II). We attach importance to this lengthy post-operative observation since the longer these patients are followed the more postoperative biliary symptoms are found.

Results in 136 cholecystectomies are classified as good, fair (improved) and poor (Table III).

It has been repeatedly pointed out that there is a marked discrepancy between the end results in cholecystitis with stones and in the stoneless gall bladder. Our series bears this out.

CHOLECYSTITIS WITH STONES

Cholecystectomy was performed in 102 patients who were found at the operating table to have stones (Table III). In seventy per cent the results were good, with subsidence of all or almost all of symptoms. In thirteen per cent the results were fair. Among the fair results there was one group in whom colic recurred with such frequency and severity that further surgery was considered, but the colic finally disappeared. In a second group colic subsided but there was residual indigestion of a biliary character which persisted over long periods. This indigestion was somewhat difficult to control. Thus eighty-three per cent benefited from the operation. In 17 patients (17%) the results were poor, colic persisting or recurring following cholecystectomy. Most of these patients were re-operated. Stones were found either in the stump of the gall bladder (1), cystic duct (2), or common duct (8). A thickened common duct (chronic cholangitis) without stones was drained for a long period in one patient. Operation revealed adhesions partly obstructing a loop of bowel in two patients. A clinical diagnosis of biliary tract infection was made in two patients and biliary dyskinesia in an additional patient.

STONELESS GALL BLADDER

Cholecystectomy was performed in 34 patients who were found at the operating table to have no stones (Table III). In 12 patients (35%) the results were good. An additional 2 patients (6%) had fair results,

making a total of forty-one percent who improved after operation.

Of the twenty patients who did not benefit from cholecystectomy for stoneless gall bladder, the subse-

TABLE III
Results of cholecystectomy

	Calculus Gall Bladder	Stoneless Gall Bladder
Good Results		
1. Subsidence of all symptoms.	38	2
2. Subsidence of all symptoms except spastic constipation.	8	
3. Subsidence of all symptoms except duodenal ulcer.	7	4
4. Subsidence of colic, residual symptoms of 'ulcer-like' character, no ulcer demonstrated.	3	3
5. Subsidence of colic, residual mild biliary indigestion for short periods, with some food idiosyncrasy, symptoms easily controllable by dietetic and anti-spastic management.	16	3
	<u>72 patients</u> or 70%	<u>12 patients</u> or 35%
Fair Results		
1. Improved but in the first 3 years after operation colics appeared frequently, finally disappeared.	4	1
2. Subsidence of colic, residual indigestion of biliary type persisted over long periods, symptoms somewhat difficult to control.	9	1
	<u>13 patients</u> or 13%	<u>2 patients</u> or 6%
Poor Results		
1. Persistent colic and indigestion due to stone in cystic duct (2), stone in gall bladder stump (1), stone in common duct (7), stone in common duct plus ulcer (1), thickened common duct (chronic cholangitis) (2), probable cholangitis (2), post-operative adhesions (3).	14	4
2. Persistent colic and indigestion of probable biliary origin, (clinical diagnosis).	2	5
3. Persistent colic and indigestion of undetermined origin (biliary dyskinesia).	1	2
4. Persistent indigestion of extra-biliary origin, (neurosis) (2), gastro-intestinal allergy (1), TBC (1), pyelonephritis (1), duodenal ulcer (4).		9
	<u>17 patients</u> or 17%	<u>20 patients</u> or 59%
TOTAL	<u>102</u>	<u>34</u>

quent course suggests that nine perhaps should not have been operated. They were subsequently found to have extra-biliary conditions as neurosis, gastro-intestinal allergy, endocrinopathy, pelvic tuberculosis, etc. In the opinion of some, these nine patients should be excluded from a survey of end results and should be charged off as errors in diagnosis. We cannot agree with this standpoint. Although in retrospect there may have been a questionable indication for operation, decision to operate was based on the condition that presented itself at that time. We studied some of these patients for several years and surgery was finally resorted to after most careful deliberation. The group

in whom the postoperative course suggests poor selection of cases for operation will continue to be a problem for the practitioner and will contribute to the high incidence of poor results in gall bladder surgery.

The causes of failure in the remaining eleven were biliary in nature: thickened common duct (chronic cholangitis) (1); probable cholangitis (2); post-operative adhesions (1); persistent colic and indigestion of biliary origin (5); and persistent colic and indigestion of undetermined origin (biliary dyskinesia) (2).

PROGNOSIS FOR RELIEF FROM OPERATION

Improvement after cholecystectomy for stones being about twice as frequent as in the stoneless cases it is necessary to bear in mind that the presence or absence of stones in any particular case may be unpredictable. The decision to operate is made on the basis of clinical symptoms the most important of which is colic. In 119 patients where colic was present pre-operatively seventy-six per cent were benefited by the operation. In the 17 patients where no colic was present, only forty-one per cent benefited from the operation. Where no pre-operative colic was present and no stones found at operation, surgery was almost uniformly unsuccessful, ten of eleven cases receiving no benefit. This latter group constitutes the worst group from a prognostic standpoint.

Graham and Mackey (1) point to the frequency of errors in diagnosis as a cause of failure to relieve the patient's symptoms. They point out that many common conditions are often confused with gall bladder disease, particularly with the less severe forms of cholecystitis. Errors in diagnosis contribute a considerable proportion of failures in stoneless gall bladder.

COMPARATIVE FIGURES ON END RESULTS

Others (2, 3, 4, 5, 6)* have reported good results from cholecystectomy in calculous cholecystitis averaging 80%-85%.* Our end results (83% benefited) is in agreement with the prevailing opinion here.

In non-calculous cholecystitis, however, there is decided disagreement in the percentage of relief to be expected (1, 2, 3, 4, 6, 7, 8, 9, 10). Figures vary from 85% to 53%,* the latter quoted by Stanton (10). The reports of Cattell (8), Graham and Mackey (1), Maynard (4), Wilkinson (9) and Wilson, Lehman and Goodwin (6), are all in the neighborhood of 65% benefited. Our series (41% benefited) is the lowest we have encountered thus far.

II

CAUSES OF RECURRENT SYMPTOMS OF BILIARY TRACT ORIGIN

1. *Common Duct Stones* were present in 8 cases. In a few the common duct stone was probably present but was overlooked at the time of the cholecystectomy. In others stones formed in the biliary tree after cholecystectomy. For instance one of our patients had cholecystectomy with removal of stones, no stones being palpated in the common duct. Colic recurred and 3 months after the cholecystectomy the common duct was opened, stones removed, and a T tube inserted.

*All figures quoted, including ours, refers to the percentage benefited among the surviving patients. As our series was composed of patients studied clinically an average of 7½ years post-operative, we have excluded post-operative deaths and untraced cases from the figures quoted in Articles 1 to 11 inclusive. Inclusion of the patients who died would decrease the percentage benefited by as much as 5%.

Three years later a third operation was performed for recurrent colic and stones were again removed from the common duct. Colics have recurred since the third operation and re-operation has been advised. This is a pronounced example of a "stone-former" or stone diathesis.

2. *Cystic Duct Stone* caused recurrent colic in 2 cases. There were two additional instances in which a stump of the gall bladder was found at the secondary operation. In one of these latter there had been a re-formation of stones.

3. *Thickened Common Duct (Chronic Cholangitis)*: In two patients who had frequent and severe recurring colics after cholecystectomy, secondary operation disclosed a thickened common duct but no stones. The common duct was thickened probably because of chronic cholangitis. Prolonged T tube drainage permanently relieved one patient and gave only temporary relief to another.

4. *Residual Biliary Indigestion (Residual Biliary Tract Infection?)*: Residual indigestion, biliary in type was present in 29 patients (21%) after cholecystectomy. These are listed in Table III (Good results, item 5: Fair results, item 2). Distress was confined to the epigastrium and came immediately after meals with belching, distension, food selection, and idiosyncrasy to fatty foods. The distress was similar to that present pre-operatively between attacks of colic. There was incomplete relief from bowel management, although some of these patients were constipated. Duodenal drainage was done on a number of these patients to determine the presence of cholesterol crystals, calcium bilirubin pigment, bile stained pus cells, etc. Flat plate studies of the bile passages and gastrointestinal studies were done. The patients were observed for icterus by clinical and chemical methods, and for fever and leukocytosis. None of these examinations gave diagnostic information as to the cause of the indigestion in this group of patients. It is our opinion, however, that this residual indigestion is due to infection in the biliary tree or the sequelae of infection, resulting in malfunction of the bile ducts, liver or pancreas.

Various theories have been proposed to explain this group of symptoms:

(a) Hepatitis. Ravdin Riegel Johnston and Morrison (11) have demonstrated that diminution of bile salts occurs with biliary tract disease. In the hepatitis of biliary tract disease of long standing the bile salts, which play such an important role in the activation of lipase and in the digestion and absorption of fats are definitely reduced in concentration. Agrifoglio (12) demonstrated a decreased utilization of fats, chiefly soaps and fatty acids in the cholecystectomized dog. This decrease appeared within 90 days. After 10-15 months the utilization of fats except soaps improved. This corresponds to the clinical picture in humans, in whom post-operative indigestion finally clears up.

(b) Cholangitis (Scott (13)). (c) Biliary Stasis (Green, Twiss, Carter (14)) (Brown and Dolkart (15)). (d) Spastic biliary tract (Kunath (3)). (e) The gastric catarrh which may be present in a progressing cholecystitis may persist after cholecystectomy (Deaver and Bortz (2)). (f) Spastic or irritable colon (Wilkinson (9)). (g) Biliary Dyskinesia.

5. *Biliary Dyskinesia*: A recent concept is that motor disorders of the extrahepatic biliary passages may produce the symptoms of gall bladder distress or

colic in the absence of stone or inflammation. The historical development and physiologic basis for this so-called biliary dyskinesia has been recently summarized by Ivy and Sandblom (16). They suggest that the presence of an irritable or hypertrophied sphincter of the common duct may explain the recurrence of symptoms in some patients following cholecystectomy.

Biliary colic occurs not infrequently soon after cholecystectomy, resulting in the so-called convalescent colic. The loss of the reservoir function of the gall bladder causes compensatory dilatation of the larger bile ducts and there is derangement of the emptying mechanism. McGowan, Butsch and Walters (17) measured the common duct pressures post-operatively and demonstrated a rise in the intraductal pressure during these attacks of colic. Following the inhalation of amyl nitrite the pressure fell and the colic was relieved. These colics, coming on during the first six months of the post-operative period, frequently are a source of worry. If the common duct has not been opened at the time of operation, one should think of convalescent colic as well as over-looked stone. Differential diagnosis between convalescent colic and common duct stone can sometimes be made on the fact that with stone there may be fever, leucocytosis or icterus. A flat plat of the abdomen may be of value. Duodenal drainage may reveal calcium bilirubin pigment or cholesterolin crystals. In some cases it is impossible to differentiate the two conditions. Re-operation must not be hastily done. If the attacks of colic are infrequent and not severe it is advisable to postpone operation for as long as a year. Several of our patients had subsidence of colic within this length of time. Weir and Snell (18) state that these post-operative or "convalescent" colics are usually less severe than the pre-operative colic, that they become progressively less painful, and finally clear up. When the attacks persist and the patients are re-operated and no stones are found, Judd (19) advocates prolonged drainage of the common duct with a T tube. This gives symptomatic relief.

Two of our cases of recurrent colic of undetermined origin were thought to be due to biliary dyskinesia occasioned by the activity of a duodenal ulcer. Both of these patients had the gall bladder removed for cholecystitis. In one, stone was present; in the other it was absent. Duodenal ulcer was later demonstrated by X-ray in both instances. On ulcer management there was subsidence of colic with occasional recurrence of ulcer indigestion.

That biliary dyskinesia can also be due to disorders of the sympathetic nervous system has been suggested by Weir and Snell (18). For instance, one of our patients, intensely neurotic, had removal of gall stones without removal of the gall bladder. Later there was recurrence of colic of such a nature that at times it was difficult to determine if the attack was organic or functional in origin. A chronically infected gall bladder without stones was removed. The severe colic persisted. Careful re-examination including two hospital admissions failed to reveal evidence of common duct stone. She has an intense anxiety neurosis and recurrent colics are related to domestic difficulties.

The concept of biliary dyskinesia is necessary to explain recurrent severe biliary colic in several of our patients who had no demonstrable evidence of calculus or inflammation in the biliary tree. Biliary dyskinesia may be looked upon as a functional disturbance due to

spasm of the sphincter of Oddi which may result from cholecystectomy, duodenal ulcer or neurosis.

III

EXTRA-BILIARY CAUSES FOR SYMPTOMS AFTER CHOLECYSTECTOMY

Residual symptoms after gall bladder operations may be due to several causes not related to the biliary tract:

1. *Intestinal adhesions* with partial intestinal obstruction was the cause of recurrent attacks of colic in only two of our cases and of recurrent indigestion in an additional one. In the two cases with colic the pre-operative diagnosis was common duct stone. No stones were found at operation. Adhesions obstructing a loop of small bowel were freed with complete relief of symptoms. The case with indigestion persisting after cholecystectomy was re-operated six years later and a patent common duct, without stones was found. Adhesions, however, were separated, since which time she has had symptomatic relief. Intestinal adhesions are often blamed for recurrent pains following cholecystectomy, but are usually an inadequate or incorrect explanation of the symptoms. Adhesions cause symptoms if the bowel is obstructed or there is interference with the motility of the intestinal tract. All in all, one must be very cautious in ascribing a colic to postoperative adhesions.

2. *Spastic Colon Associated with Biliary Tract Disease:* Spastic colon was noted in 46% of our cholecystectomized patients. Table III lists only 8 cases (6%) as having spastic colon. When more important residual symptoms were present, the added presence of spastic colon is not noted in the table. Rehfuess and Nelson (20) report an incidence of 75% of spastic constipation in gall bladder disease.

In many patients spastic colon caused epigastric indigestion which could be easily confused with that of biliary origin. It is important to recognize that spastic colon may mimic biliary tract disorders. The similarity in symptoms of chronic cholecystitis and irritable colon has been pointed out by Wilkinson (9). Epigastric distress, gas, belching, pain in the upper abdomen, and constipation are present in both conditions. Even cholecystography will not distinguish between these two diseases as Lahey and Jordon (21) have shown that 44% of the patients with chronic dyspepsia whose gall bladder cannot be visualized after the administration of dye will later show normal filling after an adequate period of bowel management.

Bowel management, with bland diet, antispasmodics as belladonna, sedatives as phenobarital or bromide, local heat, and use of hot water or mineral oil or oil enemata will often clear up indigestion in a cholecystectomized patient.

3. *Peptic Ulcer:* In the cholecystectomized group of 136 patients, 15 had duodenal ulcer, an incidence of 11%. In addition 7 cases (5%) had a clinical diagnosis of peptic ulcer, although no ulcer was demonstrated roentgenographically. These patients had typical post-prandial distress, complete relief with ulcer management and recurrences from time to time.

Of the 15 definitely proved ulcer patients the ulcer was known to be present previous to cholecystectomy in 3. At operation two had calculous cholecystitis and one non-calculous cholecystitis.

In 10 patients indigestion persisted after cholecystectomy. The cause for this was later demonstrated to

be due to ulcer. Four of these patients were found at operation to have calculous cholecystitis, the remaining 6 non-calculous cholecystitis.

In the remaining 2 patients all gastro-intestinal symptoms disappeared following cholecystectomy. However, 1 and 9 years after the cholecystectomy indigestion recurred which was demonstrated to be due to ulcer. One had calculous cholecystitis and one non-calculous cholecystitis.

To summarize the 15 patients with ulcer, 7 had calculous cholecystitis and 8 non-calculous cholecystitis.

Laird (22) reports an incidence of 4.8% of peptic ulcer in 250 consecutive patients who underwent cholecystectomy. He points out that the incidence of ulcer with cholecystitis is not markedly higher than the percentage of ulcer found in the general population and concluded there is no close inter-relationship between the two diseases. McVicar and Wer (23) found the two diseases associated in 4.1%. Bruce (24) found an incidence of 6% in 100 consecutive cases and he concludes the coexistence of cholecystitis and duodenal ulcer is not rare. He advocates a careful examination of the duodenum when operating for gall bladder disease. Judd (25) emphasized the importance of cholecystitis in bleeding duodenal ulcer.

The incidence of 11% of ulcer in our series of cholecystitis is considerably higher than reported by others. The high incidence is possibly due to the following factors:

a. Our figures include not only the ulcers found at the cholecystectomy but also those that developed during a follow-up period averaging seven and one-half years.

b. There may be a common focus of infection in the portal area, or an infection of one organ may drain to the other organ via the lymphatics.

c. Mistakes in diagnosis. In the eight patients with non-calculous cholecystitis and even in the 7 calculous cases one could take the viewpoint that the ulcer was a more important cause of symptoms than the gall bladder disease and that the treatment should have been directed at the ulcer rather than the gall bladder.

Patients with peptic ulcer or pre-ulcerous dyspepsias may have symptoms mimicking gall bladder disease. In every large clinic not a few patients with undiagnosed duodenal ulcer have gall bladder operations. An obese sthenic woman with upper abdominal dyspepsia and pain suggestive of biliary colic presents herself. Physical examination reveals no differential information. The Graham-Cole test reveals a poorly functioning gall bladder. Unless the X-ray examination includes the upper intestinal tract, a duodenal ulcer may be overlooked and operation for cholecystitis advised. Miller (26), Pancoast (27) and others have pointed out that the irritable duodenum of ulcer or duodenitis frequently gives rise to a faint or absent gall bladder shadow due to lack of closure of the sphincter of Oddi. A second reason for failure to diagnose ulcer in these cases is that the presence of colic focuses attention away from ulcer and on the gall bladder.

Wilkie (28) has described attacks of acute pain suggestive of biliary colic in patients who on accurate investigation or operation prove to have a chronic duodenal ulcer. He terms this combination of symptoms "cholecysto-duodenal syndrome" and states that 10%

of female patients referred to him in hospital practice for cholecystectomy were in fact suffering from duodenal ulcer.

The high ulcer incidence in gall bladder disease brings up two practical points:

(a) Ordering a cholecystogram without an accompanying examination of the upper gastro-intestinal tract may bring one to diagnostic grief.

(b) In patients who have indigestion after cholecystectomy, whether ulcer is demonstrated by X-ray or not, it always pays to try diet-alkali management for ulcer. Not infrequently patients who have post-operative indigestion which cannot be relieved by gall bladder diet, cholagogues and antispasmodics, obtain relief from alkalis. The finding of duodenal ulcer in a patient who has had cholecystectomy does not signify that the cholecystectomy was unnecessary.

4. *Anxiety Neurosis*: Only two patients are listed in Table III as having poor results following cholecystectomy because of anxiety neurosis. In these two the neurosis dominated the clinical picture both before and after operation and in retrospect there was perhaps a poor indication for cholecystectomy. However, 25% of patients of the entire group (see Table IV)

TABLE IV

Associated diseases in 165 patients with biliary tract operations

Duodenal ulcer	12%
Ulcer syndrome (X-ray negative for ulcer)	4%
Spastic Colon	41%
Post-operative Hernia after Cholecystectomy	8%
Endocrine Disorders	
(a) Menopausal symptoms	16%
(b) Hypothyroidism and thyroid adenoma	5%
(c) Hypopituitarism	1%
(d) Obesity	8%
Diabetes mellitus	4%
Essential hypertension, coronary disease and their complications	22%
Arthritis	35%
Anxiety Neurosis	25%

had anxiety neurosis. The more unstable the patient the more likely will she give audience to trivial residual symptoms. In general the clinic patients and the Jewish patients predominated in this group. Deaver and Bortz (2) found that highly neurotic persons often exhibit a continuance of symptoms even after removal of a definitely diseased gall bladder, and many patients in their series complaining of persistence of symptoms were of this type.

5. *Gastro-intestinal Allergy* was shown to be the cause of residual symptoms in two cases. One patient of an allergic family, had an eczema for years, had dyspeptic symptoms before and after operation. Skin tests were positive to many foods, but some of the foods she was positive to on skin test could be tolerated in her intestinal tract. Elimination diet by trial and error methods and drug treatment gave complete subsidence of symptoms. Dietary indiscretions caused immediate return of symptoms.

6. *Diseases of distant organs* may cause symptoms

simulating biliary disease. In two of our patients there was epigastric indigestion thought to be biliary in origin. From each a stoneless gall bladder with a minor degree of pathology was removed. Post-operatively the indigestion was unchanged. Investigation disclosed one case to have pelvic tuberculosis, the other pyelonephritis.

7. *Endocrine disorders*, especially menopause, were found to be of great importance, probably because they make the patient more irritable in both the cerebral and visceral zones.

RESULTS OF CHOLECYSTOSTOMY

31 patients underwent 34 cholecystostomies, three of the patients having two cholecystostomies each. Only 5 of the 31 patients (16%) obtained relief of colic and indigestion. 14 later underwent cholecystectomy because of recurrence of colic. An additional 4 should have been re-operated for recurrent colic, but operation was refused or contraindicated. Thus in 18 patients (58%), there was severe recurrent colic. In 7 patients (23%) there was relief of colic but persistent recurrent indigestion.

Our figures in no way represent what may be expected from cholecystostomy, as our series includes a large number of patients who had cholecystectomy after failure of relief from cholecystostomy. Christopher (29) states that 50% of patients who had cholecystostomy had no subsequent biliary distress. 25% of his series had mild residual symptoms and 25% had severe symptoms. Half of this last group were later submitted to cholecystectomy.

Cattell (8) reported 71.7% of patients unimproved after cholecystostomy, in half of whom secondary operation was necessary.

EXPLORATORY OPERATIONS ON THE GALL BLADDER

In twelve patients with a pre-operative diagnosis of chronic cholecystitis, exploration revealed insufficient gross evidence of gall bladder disease to warrant removal. Duodenal ulcer was found at operation or diagnosed subsequent to operation in six of these patients. The course of an additional three patients substantiated a diagnosis of anxiety neurosis and spastic constipation. The course of the remaining three showed these patients to have cholecystitis.

In four of the 12 patients who were explored but no cholecystectomy done, there was recurrence of symptoms of sufficient degree that a secondary operation of cholecystectomy was performed. Two of these had colic previous to the secondary operation, two had persistent indigestion. The only one who had cure of symptoms was one in whom stones were found.

It is important to carefully survey the patient clinically and roentgenologically before operation. The criteria for operation consist clinically in the presence of colic and positive roentgen evidence. When both of these criteria are fulfilled and the surgeon encounters a normal looking gall bladder without stones and no other lesion is found, a difficult problem of operative judgment presents itself. Many surgeons feel that if there is a definite history of biliary colic and positive roentgen evidence of cholecystitis, cholecystectomy is warranted (Stanton (10), Lahey (30)).

IV

ASSOCIATED DISEASES

Table IV shows the incidence of those diseases most commonly associated with cholecystitis.

333 associated diagnoses were recorded in the 165 cases, or an average of 2.4 per patient. Adding the gall bladder disease each patient had 3.4 diagnoses. A previous study of clinic patients suffering from gastrointestinal disorders by Meyers and Sandweiss (31) showed an average of 4.4 diagnoses per patient.

The incidence of diabetes mellitus (4%) is low compared to the figures of Johnston (32) who reports an incidence of 7.2% of diabetes in 194 cases of gall bladder disease.

Menopausal symptoms were present in 16% of cases. The remainder of endocrine disorders were chiefly concerned with fat metabolism. Hypothyroidism was present in 5% of our series, hypopituitarism in 1% and obesity in 8%.

Degenerative cardiovascular diseases, as essential hypertension and its sequelae, and coronary sclerosis and thrombosis forms a definite group (22%). There is some relation here to the age of the patient but the figures show that degenerative vascular disease and cholecystitis are commonly associated.

Arthritis, present in 35% of the cases, was practically always hypertrophic in type. Rehfuess and Nelson (20) report an incidence of 44% of muscle or joint involvement in 125 patients who had had gall bladder surgery.

Anxiety neurosis was common (25%). No causal relation to the cholecystitis is considered here.

The incidence of post-operative hernia in the cholecystomized group was 8%, after all biliary tract operations 9.5%.

An interesting hypothesis to explain the co-incidence of the above associated diseases is as follows: The patient is obese, due purely to overeating or with an endocrine disorder, as hypothyroidism, hypopituitarism or menopause as a contributing factor. The body's ability to handle fat is impaired. Cholesterol is deposited in the gall bladder wall or lumen in excess amounts. This initiates stones and later infection. The vascular disease may result from obesity with increased strain on the heart, or deposit of products of abnormal fat metabolism in the vessel wall, or contraction of vessel wall due to endocrinopathy. The hypertrophic arthritis may be due to a metabolic disturbance or obesity.

LIFE TIME NATURE OF BILIARY TRACT DISEASE

When a patient presents herself with the usual symptoms and objective findings of gall bladder disease and a cholecystectomy is recommended, the patient expects (and so does the physician) that following removal of her gall bladder she will be symptomatically and actually well. The patient draws an analogy to appendicitis, once the offending gall bladder or stones are out she will be perfectly well. This expectation was realized in only half of our cases (54%). It is important if we are not to leave a false impression to think of the disease as affecting not only the gall bladder but the entire biliary tract. Removal of the gall bladder may remove the chief seat of inflammation, and removal of the gall stones may remove the source of much of the colic. Operation will not, however, remove the inflammation in the biliary

ducts, liver and pancreas, nor affect the metabolic disturbance which may have been the cause of stone formation. In fact, it may precipitate motor disturbances of the sphincter of Oddi or biliary tree.

One is impressed with the fact that the longer one follows cholecystectomized patients the higher is the incidence of biliary tract sequelae. A patient may do pretty well after a cholecystectomy, then two or ten years after operation colics may recur. Or a patient who has been eating everything finds that careful food selection is necessary to prevent indigestion. With the concept of the life time nature of the disease in mind, one should supervise a patient after cholecystectomy instead of allowing her to assume that she will have no further difficulties.

That gall bladder disease may be merely a link in a chain of related disturbances is suggested by the following:

1. The life time nature of biliary tract symptoms.
2. The frequent repetition of certain associated diseases as arthritis, cardiovascular disease, diabetes, etc.
3. The frequent association of metabolic and endocrine factors as hypothyroidism, hypopituitarism, obesity, pregnancy, menopause, hypercholesterolemia.
4. The appearance of gall bladder disease in a patient of a certain constitutional type, the majority being in those of sthenic habitus.
5. Despite definite biliary tract symptoms and findings pre-operatively, at operation the gross pathology may be found to be slight.

May not "gall bladder disease" be merely one phase of a more fundamental and more inclusive disturbance, the nature of which we now have only fragmentary knowledge? If this is true cholecystectomy may give relief only by breaking the chain at a certain phase, with the possibility of recurrence of similar or other type of symptoms.

TREATMENT

The selection of patients to be operated is of great importance. The most favorable patients for cholecystectomy are those having colic due to the presence of stones demonstrated pre-operatively, or patients with colic who have a non-functioning gall bladder. The most unfavorable cases are those in whom indigestion but no colic was present pre-operatively and regardless if stones were demonstrated pre-operatively.

Medical management commencing immediately after operation will yield more satisfactory results than leaving the patient to his own devices in the post-operative period. Usually some dietetic supervision and regulation of the bowels is all that is required. When recurrent symptoms appear after cholecystectomy a complete survey should be made of the patient to determine the nature of the biliary lesion as well as to detect the presence of such extra-biliary lesions as duodenal ulcer, spastic colon, anxiety state, etc. Study of the patient for the presence of such associated diseases as coronary disease, diabetes mellitus, arthritis, etc., is important.

B. B. Vincent Lyon has epitomized the treatment of biliary tract disease as diet, drugs and drainage. A bland diet is prescribed, low in fat if the patient is obese, higher in butter, cream and eggs if the patient has been undernourished.

Drug treatment includes cholagogics as bile salts or their derivatives. Anti-spasmodics as belladonna and

sedatives as phenobarbital or bromides are very useful. Determination of gastric acidity with the judicious use of alkalis or hydrochloric acid may give additional relief for the feeling of epigastric distention. Regulation of the bowels without the use of irritant cathartics is important.

In addition some medicine to combat attacks of pain may be necessary as a capsule of codeine and aspirin, a suppository of opium and belladonna or an occasional hypodermic of morphine. Recently Walters (17) has advocated the use of amyl nitrite and aminophyllin in colics after cholecystectomy, which he states are more efficient than morphine in opening the common duct sphincter with consequent fall of the intraductal pressure. The above pain-lulling remedies are particularly needed in convalescent colic and biliary dyskinetic attacks.

Duodenal drainage may be helpful. Removal of foci of infection and daily exercise should be prescribed.

The endocrine and metabolic feature of the individual case may require treatment.

Often the crucial point in relieving symptoms will be the administration of thyroid extract which decreases weight, adds to intestinal tone, relieves constipation and adds to the general feeling of well-being.

Many of these patients are of a neurotic make-up and in the presence of some indigestion forget about the pre-operative colic and its subsidence following operation. Treatment for migraine, menopausal symptoms, assurance that a secondary operation will be unnecessary and moral support are indicated.

SUMMARY

A series of 165 patients who had 199 operations for biliary tract disease were studied on the average 7½ years after operation.

I. *End results of cholecystectomy.*

In a series of 136 patients who underwent cholecystectomy, 83% of those with calculous cholecystitis benefited from the operation and only 41% of those with non-calculous cholecystitis benefited.

Where pre-operative colic was present and regardless if stones were found at operation, 76% benefited from cholecystectomy; with no pre-operative colic, only 41% were benefited.

II. *Causes of recurrent biliary symptoms in cholecystectomized patients.*

The causes for symptoms of marked degree include: residual biliary tract infection, biliary dyskinesia, common duct stones, chronic cholangitis and cystic duct stones.

III. *Extra-biliary causes for symptoms after cholecystectomy.*

(a) Mistakes in diagnosis. Long after cholecystectomy was performed the distress for which operation was performed was thought in retrospect to be due to one of the following conditions: peptic ulcer, neurosis, gastro-intestinal allergy, pelvic tuberculosis, pyelonephritis.

(b) Appearance of abdominal symptoms due to new pathology. Patients who have undergone cholecystectomy are not immune to the general run of gastro-intestinal diseases as duodenal ulcer, spastic colon and intestinal adhesions or to such general conditions as anxiety neurosis and endocrinopathy. These conditions may give biliary-like symptoms.

IV. *Associated Diseases.*

An average of 3.4 diseases was present in each of

our patients who underwent biliary tract surgery. The diseases most commonly associated with pathology in the biliary tract were found to be degenerative vascular disease as coronary disease and essential hypertension, endocrine disturbances as menopause, hypothyroidism, hypopituitarism and obesity, diabetes mellitus, chronic hypertrophic arthritis, anxiety neurosis and the gastro-intestinal diseases listed above.

V. The life time nature of biliary tract disease in some patients, the frequent repetition of the associated diseases listed above and the metabolic and endocrine

background so often present suggest that biliary tract disease may be only one phase of a more fundamental and more inclusive disturbance.

VI. Given a patient with a gall bladder scar and abdominal symptoms, careful analysis will show the symptoms to be due to

(a) Persistent or recurrent biliary tract disease.

(b) Extra-biliary disease, uncorrected by cholecystectomy because the original symptoms were due to pathology outside of the biliary tract.

(c) The appearance of new abdominal pathology subsequent to and independent of the cholecystectomy.

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Mycotic Infections of the Stomach

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WHILE in recent years a great deal of interest has been shown in fungi and in diseases caused by them, particularly of the skin and lungs, the fact that they may be responsible for gastric lesions has been practically ignored. An opportunity to operate on a patient with an advanced mycotic infection of the stomach (4) convinced me not only that this condition should be considered in the differential diagnosis of gastric pathology but also that an early diagnosis was desirable.

There have been reports that fungi have caused gastritis (26), ulceration (1, 11, 15, 18, 28), and even perforation of the stomach (4, 5), but such reports have been comparatively few and infrequent. Since fungi may be pathogenic, it is possible that if more frequently sought, fungi might be found to be a more common cause of gastric infections than thus far considered.

Fungi have been found in 40 per cent of the oral pharyngeal cavities of apparently healthy people (7, 20, 29). Since fungi are very prevalent in food, water

and air, it is to be expected that due to the swallowing of food and saliva, fungi may be carried to the stomach and found in the gastric contents. Although there are no reports dealing with the relative incidence of fungi in the mouth and the stomach at the same time, there are reports of fungi being present in 40 to 60 per cent of stomach aspirations (9, 10, 22). Crasset reported that he found moulds in twenty out of thirty stomachs examined after death; Zalesky (31) and Maresch (18) also found fungi in gastric contents at autopsy. Fungi have been found in stools in a correspondingly high percentage (24). The fungus most frequently found in mycotic infections of the stomach was *Monilia albicans*; in some instances, *Aspergillus* was the offending organism; and rarely the ray fungus was isolated. A positive report that fungi are present in gastric contents should be made only if there are at least 10 colonies per plate on the first culture (24).

If there is any local circulatory disturbance of the gastric mucosa, or if its immunity is lessened (29), pathogenic fungi may invade it and form thick dip-

theria-like membranes. Should there be injury or further local vascular damage, this condition may go on to ulceration (2, 3, 10, 16, 23). A typical mycotic ulcer is usually found on the lesser curvature of the stomach. At times, instead of a single ulcer, there may be multiple lesions; these ulcerations may vary in size from minute lesions to ulcerations so large that they may involve the whole stomach. Gradually such an ulceration may penetrate to the muscularis (5) or even to the serous membrane (17). In one instance (5), perforation with peritonitis resulted, and in another case (4), fistulous formation occurred after a perforation.

Pathological examination of the necrotic tissues and adjacent layers of a mycotic ulceration reveals that they are infested with moulds—branching filaments with small, bulb-like tips, lacking reproductive forms. There is very little leukocytic reaction. The base of the ulcer is made up of necrotic tissue, and there is thrombosis in the underlying vessels; the periphery of the ulcer is dark and granular and shows a hemorrhagic inflammatory reaction. In an actinomycotic ulcer of the stomach, typical sulphur bodies of the *actinomyces bovis* (ray fungi) may be found, but they are usually present only in a very limited area of the lesion (6, 14, 25, 30).

The symptoms are strikingly like those of a functional gastric disturbance or of a peptic ulcer (21); namely, pain or epigastric distress, heartburn, belching, a sense of fullness, nausea, and vomiting. There is nothing definite in the symptomatology to differentiate mycotic infections from other gastric lesions.

As far as we know, a mycotic gastric lesion has not been recognized before operation. Diagnosis has thus far been made only at operation or at biopsy.

A gastric mycotic infection should be thought of whenever the vomitus, blood-streaked or otherwise, contains strands of pathogenic moulds. Should these fungi also be found in the gastric contents that have been obtained by a stomach tube; uncontaminated by moulds that may be present in the mouth or pharynx, then a mycotic lesion should be suspected. The suspicion is further strengthened if these fungi can be cultured on acid fungus media, and the diagnosis is warranted if inoculation (29) of this culture into a rabbit results in endothelial proliferation and giant cell formation together with an abundant growth of fungi without much of any inflammatory reaction. For further confirmation of the diagnosis, positive blood agglutination and intradermal tests for *Monilia* have been used (13). Blood cultures have also been found to be positive for *Monilia* by Irish (12) in 40 per cent of his cases. In actinomycotic lesions where there is a sinus or sinuses, a diagnosis may be made from the sinus curettings which may disclose the ray fungi (19). If a patient with an unsuspected gastric mycotic lesion is operated upon, the diagnosis should be suggested if upon incising the parietal peritoneum, necrotic tissue without any frank purulent manifestations is found. It should also be thought of if a membrane is found in the stomach that can be easily removed but leaves behind a bleeding surface, or if an ulcer is disclosed that has a necrotic base and brownish irregular periphery. Should a biopsy of the suspicious tissue disclose abundant fungi, then the confirmatory tests already mentioned should be carried out.

Buchanan (8), on the other hand, doubts the value of yeast cultures in general. He advises that study be

made not only of the presence of the organisms but also of their numerous biological products—both endogenous and exogenous. However, it does seem that the finding of pathogenic moulds in vomitus that can be cultured in appropriate media, inoculation of this culture into a rabbit with a resulting characteristic mycotic reaction, positive blood cultures, positive blood agglutinations and intradermal tests, warrant a diagnosis of a mycotic infection, particularly when there is a lack of evidence of any other lesions.

We feel that the more frequent use of gastroscopy together with increasing skill in recognizing the membrane of a typical mycotic gastritis or ulceration should help to make an early diagnosis possible.

There have not been enough case reports on the subject of gastric mycosis to warrant a reliable prognosis. The few cases that did come to operation developed no complications that could be attributed to the fungi themselves. In the rare actinomycotic infection especially, the prognosis should be guarded due to the possibility that metastasis to the liver may already have taken place.

If a diagnosis of a gastric mycotic infection could be made when there is only a gastritis or an early ulceration, the treatment consists in the administration of iodides to the point of tolerance. Sodium iodide (15 grains) injected intravenously or given by mouth in a syrup of hydriodic acid has been recommended in *Monilia* infections of the respiratory tract (12) and might be equally effective in gastric mycotic lesions. Neocarsphenamine and vaccines (13)—either auto-genous (27) or a stock vaccine including many strains, as well as non-specific vaccine (typhoid-paratyphoid) (27)—have also been used. Dietary regulation has not been of any help.

In abdominal actinomycosis, X-ray treatment has been reported as being of value (19). While this was supplemented by ultraviolet irradiation, sunbaths, iodides internally, and the application of iodine to the walls of the sinus tracts, it was felt that X-ray contributed most to the recovery of patients with this condition. A combination of both X-ray and iodides should be effective.

When the ulceration becomes so extensive that perforation takes place or repeated hemorrhages result, then there is no alternative except operation.

CONCLUSIONS

1. Fungi may cause a gastritis, ulceration and even go on to perforation.

2. There are no characteristic symptoms. The complaints are similar to those in functional disturbances of the stomach or in peptic ulcer.

3. The diagnosis should be thought of when pathogenic fungi are found in the vomitus. The suspicion should be strengthened when these fungi are found in uncontaminated gastric contents and can also be cultured in appropriate media. Should the inoculation of this culture into a rabbit give a typical reaction and be corroborated by positive blood cultures, intradermal tests and blood agglutinations, a diagnosis of a mycotic infection is warranted.

4. The more frequent use of the gastroscope together with increasing skill in recognizing typical mycotic gastritis or ulceration should help to make an early diagnosis possible.

5. No reliable prognosis can be given owing to a lack of cases on which to base a definite opinion. There

were no complications that could be attributed to the fungi themselves in those cases where operation was performed. If the lesion is due to the ray fungus, the prognosis must be definitely guarded due to the possibility that metastasis to the liver may already be present.

6. In uncomplicated cases, iodides to the point of tolerance should be administered. If there are actinomycotic sinuses; then X-ray treatment should also be used.

7. For complications such as perforation or repeated hemorrhages, operation is necessary.

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Studies in Calcium Metabolism: II. Further Contributions to the Comparative Studies of the Physico-Chemical Properties of the Gluconate and Cevitamate of Calcium and of Vitamin C

By

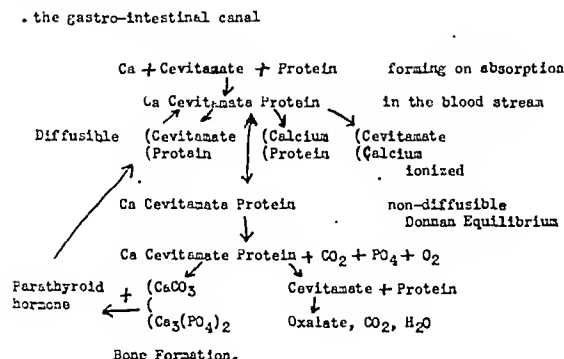
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AS a presumptive schema of calcium metabolism involving cevitic acid, the following formulas are presented:



Following the comparison of Calcium Cevitamate and calcium gluconate as to its physical properties such as solubility, ionization and depression of the

freezing point, it becomes important to observe how these substances behave in the presence of blood serum.

For this investigation the usual chemical procedures could give us no possibilities of analysis since we could not tell how much of the preparation combined with the blood proteins. This factor is important in view of the observations of the Vienna School (Pick (9), Spiro (7), Kylin (8)) that the absorption of a foreign substance introduced into the blood stream was directly proportional to its combining powers with the blood proteins. And for a substance to be utilizable by the tissues it must be bound to the blood proteins, the same being true for nutritional substances. Conversely, substances not combining with blood proteins are toxic and Jonnard has suggested this as a factor in allergy.

Fortunately, such investigation has become practical by physical analysis through the notable improvement of the interferential refractometer made by R. Jonnard (3), (in the Laboratory of Animal Biology of the University of Paris), making possible the readings

two decimal points farther than the Abbe refractometer. This improvement in technique has enlarged the scope of possibilities to include many biologic reactions described in a series of papers by Jonnard, and by Jonnard, Faillie and Zuckerkandl. In their last report from the Laboratoire de physiologic du Travail du Conservatoire des Arts et Metiers et Laboratoire d'hematologie de l' Hopital St. Louis (service due Dr. Tzanck), they describe in detail the technique and results of study of chemical reactions in the blood serum by changes in the refractive index. This has led to striking additions to our knowledge of the reactions of cholesterol, bile salts, di-iodo-tyrosine, NaCl and KCl.

The presence of Dr. Jonnard in this country on a fellowship from the University of Paris afforded the unusual opportunity of applying these methods to the study of the Calcium Salts by the principles of the Interferometric Method.

In effect, it may be stated that the index of the refraction faithfully follows the disturbances undergone by the molecular structure of the bodies under the influence of physical or chemical reactions. This makes possible rapid serial studies of biologic liquids of complex structure. The same method has likewise adduced arguments in favor of the physico-chemical constance of the protein molecules of the serum (35) a conception too little recognized. In a mixture of reagents added to the blood serum several minima may appear showing that several differently reacting substances have been added. In this manner it has been possible to study groups of bacterial antigens in one solution. The minimum of the refractive index thus shows the point of complete chemical reaction between the reagent and the blood serum.

A series of experiments were conducted; first the fixation of Vitamin C in the blood serum was studied, then the fixation of Calcium Cevitamate. A comparative study of the fixation of Calcium Cevitamate and calcium gluconate revealed an interesting difference in reaction to serum proteins. This led us to investigate the mechanism of the action of calcium and of Vitamin C in the serum. Since no study of serum calcium would be complete without investigation of the influence of the parathyroid hormone, an extended series of experiments were conducted. Some of the data tends to support the schema of serum calcium proposed in this paper and further study is planned.

FIXATION OF VITAMIN C IN THE SERUM

The interferometric method has already demonstrated that numerous substances added to the blood stream find themselves fixed in it chemically in variable amounts according to their nature, their part in the general metabolism and the pathological condition (5, 6, 7) of the blood donor. The limit of fixation or saturation point corresponds exactly with that determined by more complicated chemical or physical methods (8) in some experiments made on this subject.

If one adds progressively increasing amounts of cevitamic acid (in fresh solution in boiled distilled water) to a constant volume of serum (which in our experiments was a dilution of 83.3%), one can state that a minimum of the index of refraction occurs for a concentration of 0.5 mg. Vitamin C per cc. of serum. This was verified on seven different human sera.

These sera were from hospitalized patients not suffering from scurvy and a residual Vitamin C content must be added to our findings.

As in the case of the substances previously studied by one of us (Dr. Jonnard), there is a certain constancy between the figures found for different concentrations of serum, as is seen in the following example in which the minimum appears for 0.1 mg. per cc. of serum diluted to 16.75% or a one-fifth concentration.

C° VC	Refractive Index
0.0	1.335680
0.05 mg. per cc.	1.335615
0.1	1.335622
0.2	1.335738
0.3	1.335738
0.4	1.335756
0.5	1.335869

From what is known through previous work done with this method, it therefore seems that the serum is capable of fixing 0.5 mg. Vitamin C per cc. combined chemically with the proteins.

FIXATION OF CALCIUM CEVITAMATE

In view of these results it is interesting to see how the presence of Calcium can condition the activity of the Vitamin C on the index of the serum when Calcium Cevitamate is employed.

A first experiment made on a very small sample of serum placed the minimum index between 0.6 mg. and 1.0 mg. of product per cc. of serum.

Cone. Cal. Cevitamate	Index
0.2	1.344998
0.5	1.345321
1.0 mg. per cc.	1.345223

The same experiment repeated under the same conditions on larger samples gave results arranged in the following table:

Conc. Cal. Cevitamate	Index
0.00	1.344050
0.5	1.344812
0.6	1.344910
0.8	1.344842
1.0	1.344992
1.5	1.345223
2.0	1.345329

A very sharp minimum, therefore, appears for a concentration of 0.8 mg. of Calcium Cevitamate per cc. of serum. This is much greater than that resulting from the presence of Vitamin C. If one takes into consideration the respective molecular weights of these substances calculated from the formula one finds the calcium represents only about 9.34% of the total molecular weight. The fall of the index of the serum in the presence of this product at the amount of 0.8 mg. per cc. cannot, therefore, be attributed to the presence of calcium ions alone, particularly since the latter added alone in the form of Ca Cl_2 produces a minimum of the refraction of the serum at the amount of 0.4 to 0.5 mg. per cc. From these measurements one may say that Calcium Cevitamate possesses specific physico-chemical properties conferred by the simultaneous presence of the reacting calcium and the Vitamin C. It may be added that the phenomenon cannot be attributed either to the eventual dissociation of the

product under the influence of the dilution, for diluted in pure water its index follows a straight line:

Conc. Cal. Cevitamate (C° ccvitamate)	Index
0.2	1.333034
0.5	1.333119
1.0 mgm. per cc.	1.333218

COMPARATIVE FIXATION OF CALCIUM GLUCONATE

Referring back to the subject of this paper, it is especially striking to observe that the fixation of the calcium gluconate by the serum proteins is remarkably weaker than in the case of Calcium Cevitamate. Indeed, in the case of calcium gluconate a minimum of refraction appears for an amount of product of 0.2 mg. per cc. of serum. The trend of the phenomenon is represented in the following table summing up one of our experiments:

Conc. Final Calcium Gluconate	Refractive Index
0.0	1.343731
0.1	1.343710
0.2	1.343698
0.3	1.343735
0.5	1.343886

It is observed that up to a concentration of the product attaining .2 mgs. per cc. of serum the index varies in a noticeably regular manner. It is, therefore, possible to conclude that probably the saturation of the proteins is attained with about 0.2 mgs. of Calcium gluconate per cc. of serum. This relatively small amount checks also with the weak ionization of the calcium gluconate in our chart on the relative ionization in the first pages of this article as well as with our clinical experiences regarding the relative merit of Calcium Cevitamate as compared to calcium gluconate. The data on Calcium Cevitamate thus tends to support the conceptions of the Vienna School (Pick, Zuckerkandl, Hendl) according to which the biological activity of the products would be conditioned by their preliminary combination with the blood or tissue proteins. In our tests with Calcium Cevitamate the availability of the product is greater and more efficient since it can combine in greater quantity with the serum proteins, the intimate nature and mechanism of this combination remaining for further elucidation.

MECHANISM OF THE ACTION OF CALCIUM AND OF VITAMIN C IN THE SERUM

The question arises how these two products will reciprocally modify their behavior when they are added to it simultaneously. This point seems important to determine in order to see what part the Vitamin C may play in the metabolism of the calcium. With this in mind, we have compared in a certain number of samples of human serum at a constant concentration (83.3% for the convenience of the measurements of volume of the reagents) the index of refraction in:

- pure serum in absence of any reagent.
- serum plus 0.5 mg. of Ca CL_2 per cc.
- serum plus 0.5 mg. of Cevitamic acid per cc.
- serum plus Ca CL_2 and Cevitamic acid same final concentration.

The results are contained in the following table:

Specimen Number	Serum	Serum with Cevitamic Acid	Serum with Ca CL_2	Serum with Both Reagents
BH 12699	1.342568	1.342460	1.342453	1.342777
BH 12910	1.343484	1.343478	1.343355	1.343637
BH 12762	1.	1.343508	1.343141	1.343727
BH 12751	1.342897	1.342615	1.342726	1.343106

One sees that the two products added alone lower the index of the serum as has been previously shown, while they raise it strongly when they are added simultaneously in the same proportions. This does not occur when the same experiment is repeated by replacing the serum by the same quantity of distilled water, as is seen in the following figures:

1. Index of water used 1.333030
2. Water plus 0.5 mg. Cevitamic Acid per cc. 1.333034
3. Water plus 0.5 mg. Ca CL_2 per cc. 1.333050
4. Water plus Ca CL_2 and Cevitamic Acid same conc. 1.333058

The difference here is too weak to be attributed to a combination between the two products added by comparison with the results obtained in presence of serum. We must, therefore, admit that a combination in which the calcium and Vitamin C ions react most strongly requires, in the conditions of these experiments, the presence of blood serum and a concentration exactly that which for the two products taken separately produce the minimum of refraction, (the saturation point) of the fluid. One can also point out that the molecularly reacted Calcium Cevitamate presents a better approach to the saturation point of the serum than the addition of calcium and Vitamin C separately in unbalanced proportion. It will also be later demonstrated that the concentration of the combining elements have a definite optimum point of reaction.

One may, perhaps, assume that the reaction which in these measurements shows the important increase of index observed takes place between the new protein molecules formed on the one hand with the calcium and on the other hand with the Vitamin C, that is, calcium protein and Vitamin C protein. Although the study of the factors involved is particularly difficult, we propose to return to it further on. Nevertheless, at present let us say that to the support of this conception comes the following observation: if in the experiment, conducted in the preceding manner, the quantities of the substances added are noticeably less so that the saturation of the proteins respectively by Vitamin C and Ca CL_2 is not attained, the increase of index produced by their simultaneous presence in the serum no longer takes place, as is seen in the following example:

Serum BH 12692	C° final 83.3%.
Index of pure serum	1.342885
Serum plus 0.25 mg. Cevitamic Acid per cc.	1.342808
Serum plus 0.25 mg. Ca CL_2 per cc.	1.342812
Serum plus Ca CL_2 and Cevitamic Acid same conc.	1.342744

In this case the proteins are not saturated and the reaction is strongly concealed by the presence of non-transformed proteins capable of reacting in numerous

different ways. This explanation is comparable to that suggested by one of us (Dr. Jonnard) with F. Zuckerkandl, for the interpretation of the characteristics of the variations of the refractive index occurring in the mixture of two portions of serum, one of which was heated to 56° C. and the other kept at room temperature. In these same researches it has likewise been proven that the specific disturbance of refraction in the case of the existence of a true "zone phenomenon" evidence of a chemical reaction, were likewise concealed when the quantities of inducing products added were greater than those inducing the minimum of the index of the serum. Likewise in the case of the reaction with which we are concerned it is no longer possible to demonstrate a characteristic variation of the refractive index for any proportion of the product added if one of them is in too great quantity, as is the case of the following example:

Serum AML at 83.3% plus 1 mg. Cevitamic Acid.

C° final CaCl ₂	Index of Refraction
0.0	1.344408
0.1 mgm. per cc.	1.345119
0.2	1.344779
0.3	1.345018
0.4	1.344801
0.5	1.344931
0.6	1.345009
0.8	1.345188
1.0	1.344967

The variation of index is this time entirely irregular and shows nothing characteristic.

A composite of the findings shows the following:

We have sought to observe whether its presence can modify the reaction which appears when Vitamin C and Ca CL₂ are added simultaneously in the blood serum. With this in mind we have compared the variations of index of the serum:

(a) In the simultaneous presence of the two products mentioned.

(b) In the same case in the supplementary presence of 5 units of parathormone (Lilly).

(c) In the presence of the same quantity of hormone alone. The following are the results:

Serum BH 12751 Final conc. 60%.

1. Index of pure serum	1.342897
2. Serum plus Ca CL ₂ and Cevitamic Acid	1.343106
3. Serum plus Ca CL ₂ and Cevitamic Acid, plus hormone	1.343167
4. Serum plus hormone alone	1.343017

No characteristic phenomenon is revealed in this experiment, the same is true if one varies the quantity of hormone in presence of the same proportions of Vitamin C and of Ca CL₂, that is, respectively 0.5 mg. per cc. of each as is seen below:

1. Index of the mixture in presence of 5 units of hormone	1.339713
2. Index of the mixture in presence of 10 units of hormone	1.340018
3. Index of the mixture in presence of 15 units of hormone	1.340300
4. Index of the mixture without hormone	1.339642

In the present case the product used added in pro-

Substance	% Solution by Weight	Conc. Moles. Liter	% Ionization	Yield Ca ions per cc. Sol.	Solubility	Saturation in Serum per cc.
Calcium Cevitamate	5%	0.123	74.6	.0037	100%	
Calcium Cevitamato	10%	0.261	60.0	.0053		0.8 mg.
Calcium Cevitamate	20%	0.589	58.1	.0137		
Calcium Cevitamate	30%	1.008	55.3	.0226		
Neo-Calglucon	10%	0.125	47.8	.0048		0.2 mg.
Neo-Calglucon	20%	0.273	40.3	.0058	20%	
Calgluconate Powder	3%	0.072	48.6	.0014	3%	
Vitamin C					100%	0.5 mg.

It will thus be seen that the physico-chemical reactions check accurately with the changes in the refractive index supporting the utility of acute refractometry in the study of biologic fluids.

INFLUENCE OF THE PARATHYROID HORMONE

Regarding the possible influence of the parathyroid hormone on these reactions, advanced by one of us (Dr. Ruskin) from what is known of its part in ossification, it was interesting to study it by the same method.

gressive quantities to the serum does not seem to induce characteristic changes of the index.

Parathormone Units	Index of serum at 60% BH 12751	Index Serum BH 12737
0	1.342897	1.339642
5	1.343017	1.339642
10	1.343576	1.339642
15	1.343919	1.339642
20	1.343919	1.340441
25	1.343919	1.340700
30	1.343919	1.340864

In spite of the apparent negative results we wish to publish this experiment as suggestive of the point that the hormone does not react with the blood serum but enters into chemical relationship with the bone tissue.

SUMMARY

1. A comparative study of the solubility and ionization of Calcium Cevitamate and calcium gluconate shows the markedly greater solubility and ionization of the Calcium Cevitamate.

2. The yield of calcium ion per cc. of solution is 20 to 60 times greater for Calcium Cevitamate than for calcium gluconate.

3. The combining power of Calcium Cevitamate with serum proteins is four times greater than that of calcium gluconate, thus establishing a greater ration of utilization by the tissues for Calcium Cevitamate than for calcium gluconate.

4. A schema for serum calcium reactions is presented.

5. The saturation point of Vitamin C in human serum is established at somewhat above 0.5 mg. per cc.

6. Data is adduced towards the physico-chemical relationship of parathyroid hormone to the blood serum.

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Untoward Effects Resulting From the Use of Large Doses of Vitamin B₁*

By

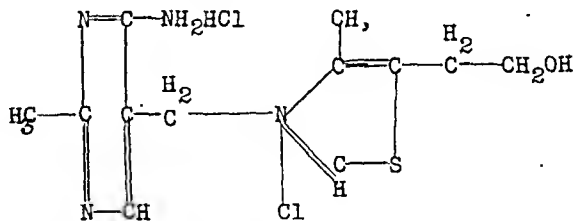
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VARIOUS uses of Vitamin B₁ have been reported since its original discovery. These have been concerned chiefly with neurological disorders. Vorhaus (1) reported its successful therapeutics in peripheral neuritis. He gave 10 mgm. daily. Lasch and Bergel (2) have reported successful management of funicular myelosis associated with pernicious anemia with the use of Vitamin B₁. Jolliffe and Jaffe (3) have reported extensive studies on the value of Vitamin B₁ in the polyneuritis caused by alcoholic addiction. Others (4) have used Vitamin B₁ in neuritis associated with pregnancy.

With the increase in availability of Vitamin B₁ since its successful synthesis in July, 1936, by R. R. Williams, more extensive clinical use is sure to follow. To date no toxic symptoms have been reported from its use. Cowgill (5) has recently stated that no toxic symptoms of any kind were observed in doses approximating 25,000 or more times the estimated daily requirement. Its chemical formula has been determined as an amine. This amine is capable of being split into a pyrimidine base, C₄ H₅ N₃ SO₂, and a sulphur compound or thiazole, C₂ H₅ NOS, by means of sodium sulphite.

The writer has been interested in the clinical investigation of B₁ in the treatment of chronic arthritis. During the past two years various preparations of Vitamin B Complex and Vitamin B₁ have been employed in the treatment of over three hundred cases of this group of diseases. During this period several definite untoward symptoms have occurred with the use of large doses of Vitamin B₁, viz: herpes zoster

has occurred in three cases. In one of these three cases, the writer was able to produce herpes on two separate occasions. This was not possible in the other



two cases because the patients refused further treatment on account of the pain produced by herpes. Symptoms suggestive of smooth muscle spasm have occurred in other cases.

PROTOCOLS

Case 1. A white female, aged 51, was first seen January 16, 1937, at which time she gave a history of typical atrophic arthritis extending over a period of twenty-six years and involving most major joints of the body. After an initial period of seven months treatment with hemolytic streptococcus vaccine, massive doses of Vitamin B₁ were given both orally and by the parenteral route, that is, 800 units of Vitamin B₁ were given orally and 2,000 units were given intravenously at weekly intervals. At the end of four weeks of such treatment, the patient complained of severe burning pain along the outer border of the right arm and the midaxillary area of the right chest. Examination revealed typical lesions of herpes zoster in these regions. The Vitamin B₁ was stopped, and the herpes

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disappeared in five weeks. Six weeks later the same dosage of Vitamin B₁ was given with similar return of the herpes zoster at the end of four weeks of such treatment. Cessation of the treatment resulted in disappearance of the herpetiform lesions in four weeks.

Case 2. A white male, aged 64, was first seen October 1, 1936, with typical hypertrophic arthritis of both hips and a lumbar spine. He was given 2,000 international units of Vitamin B₁ intravenously at weekly intervals, and this was supplemented by 800 international units of Vitamin B₁ daily by the oral route. At the end of five weeks of such treatment he developed typical herpes zoster involving the right side of the chest and the external surface of the right arm. Cessation of this treatment resulted in complete disappearance of the herpetiform lesions in three weeks.

Case 3. A white male, aged 58, was first seen November 22, 1935, with infectious arthritis involving both knee joints, duration eight months. During the Fall of 1936 he was given 1200 international units of Vitamin B₁ daily by the oral route. At the end of two months of such treatment he developed typical herpes zoster involving the right upper abdomen. Cessation of such treatment resulted in disappearance of the lesions at the end of two months.

Two other untoward symptoms have been noted in my clinical experience. In one patient nausea developed a few minutes after administration of 2,000 international units of Vitamin B₁ intravenously. This patient had been receiving 800 units of Vitamin B₁ orally for a period of six months. During the latter two months of this treatment, he had also received 2,000 units intravenously twice weekly. No untoward results were noted until the eighth week of the parenteral treatment. In addition this patient noted a sense of fullness in the epigastrium and a sense of con-

striction of the throat within two minutes after receiving the Vitamin B₁ intravenously. Another patient has noticed a sense of constriction in the throat and severe cramps when given 2,000 units of Vitamin B₁ intravenously. The latter patient developed this untoward effect after several months medication with the pure Vitamin B₁. Both these cases suggest either a sensitivity developing towards Vitamin B₁, or else that supersaturation of the tissues of the body with Vitamin B₁ may cause the untoward symptoms noted.

The above case histories would seem to indicate that large doses of Vitamin B₁ are capable of irritating the peripheral nerve plates. Apparently, this toxic symptom occurs in only a very small percentage of cases treated with massive doses of Vitamin B₁. In my own series it is less than one per cent (1%). However, one should be on guard in the use of this substance, and when an individual so treated begins to complain of intense burning pain in an unsuspected area, the administration of this vitamin should be stopped.

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Melanosis Proctocoli

Preliminary Report of Twelve Cases*†

By

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MELANOSIS proctocoli may be defined as a morbid condition of the large bowel characterized by the deposition of black or brown pigment in the mucous membrane, usually without any inflammatory process.

First referred to by Cruveilhier in 1829 (1), this disturbance of the bowel is worthy of consideration in that it is encountered occasionally during routine sigmoidoscopic examination, at operation and at necropsy. Virchow offered a brief description in 1847 (2) and called it "melanosis coli," while Solger (3) applied the term "colitis pigmentosa." By means of the sigmoidoscope, Pick in 1911 (4) recognized this medical curiosity as a distinct entity, and in his writings referred to it as the "brown bowel."

Melanosis proctocoli occurs in approximately .25 per

cent of patients examined sigmoidoscopically. It is more common in the male sex and between the ages of 30 and 50.

Various divergent and confusing hypotheses have been promulgated so far as the cause of colonic melanosis is concerned, and because the evidence is not conclusive it seems expedient to mention briefly some of the more important ones. The most significant and influential factors in the etiology are chronic intestinal stasis and the use of anthracene cathartics over a long period of time. That the latter plays an important role was first mentioned by Bartle (7). It is now generally conceded that chronic constipation is a contributing but not an initial etiologic factor, and that the pigmentation accompanies but does not cause the intestinal stasis. Bockus (8) contends that the deposition of pigment probably results from the phagocytosis of the pigment of the anthracene group. Chief among this group of cathartics is cascara, although

*Read before the "Proctologic Society," Graduate Hospital, University of Pennsylvania, December, 1937.
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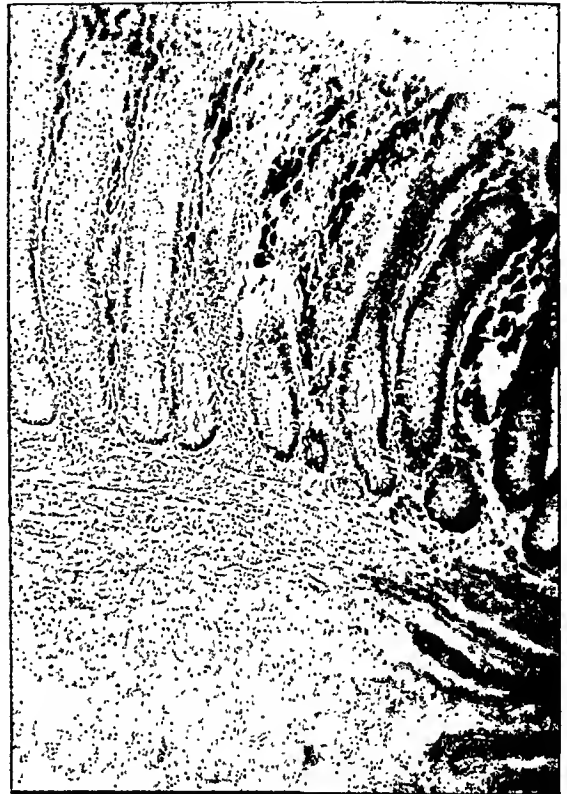
senna, aloes, rhubarb and frangula have been mentioned as offenders. Virchow described the pigmentation as a hemochromatosis. Pick was of the opinion that it was due to the products of protein disintegration, which were acted on by tyrosinase ferment and converted into melanin. Hueck (9) brought forth the theory that the pigment does not belong to the melanin group but is a lipofuchsin; further, that the splitting of certain products of digestion gives rise to a "propigment" of a lipid nature, and this is affected by ferments, giving rise to the pigment. Synnott (10) attributed the condition to the metabolic pigment melanin, which is an autochthonous substance originating in loco by transformation of preexisting material. Obendorfer (11) explains the pigmentation on the basis that disturbances in protein metabolism may result in excess production of waste products. At an early date the ingestion of heavy metals, especially mercury and lead, was thought to be the cause (12, 13). Lignac (14) believed the condition to be due to hemorrhage with subsequent bacterial activity, while McFarland (15) adhered to the theory that the pigment was formed by an enzyme which acts on the intracellular substance of the stroma of the intestinal mucosa.

Lynch (16) considers it to be due to a disturbance in the chromogenic function of the liver.

So far as the pharmacognosy is concerned many of the vegetable laxatives contain principles closely allied to methylanthraquinone or glucosides which yield such substances on hydrolysis. Cascara belongs to this group whose activity depends upon the presence of one or more oxides of methylanthraquinone. The active principle of cascara as well as aloes, and frangula appears to be emodin, $C_{15}H_{10}O_2$ or trioxymethylanthraquinone.

Any portion of the colon from the ileocecal valve to the anorectal line may be the seat of the pigmentation. As would be expected, the greater number of cases are observed in the rectum and sigmoid by gastro-enterologists and proctologists. Bockus (17) found the pigmentation most intense in the rectum, diminishing from below upward. The color of the mucous membrane is somewhat variable, not only in different patients but in the same patient. It may be evenly distributed over a large area of the rectum or arranged in a patchy manner throughout. In a series of twelve cases, seen by the authors, only one was more or less uniformly involved. A deep reddish-brown or mahogany color is usual, although an inkish-black is not altogether uncommon. These pigmented areas are broken up into minute islands, polyhedral in shape, by fine yellow or light brown striae extending in an irregular fashion. The appearance is often likened to a toad's back (18), crocodile or snake skin (2), or a chow dog's tongue (7). It is quite apparent that the existence of inflammatory changes is entirely independent of the melanosis (8). Pick, in his report (4), is quite emphatic in this respect and remarks, "in the cases studied there were no secondary inflammatory changes, no ulcerations, scars or catarrhal states of proliferation." It has been mentioned that melanosis is much higher in carcinoma of the colon (19), although the writers have found but one such case in the literature, that of Bland-Sutton (20, 21).

The granules of pigment, which vary from 7 to 20 microns, are found within large mononuclear cells in the tunica propria. According to Zobel and Susnow



Photograph of a longitudinal section of rectal mucosa, showing dark brown and black areas of pigmentation in the tunica propria between the glands. A few areas of smaller size may be seen in the submucosa.

(22) the pigment is in the mucosal villi in mild cases, and in the advanced, in the region of the muscularis or scattered through it. Infrequently they may be seen in the submucosa (10) and in the mesocolic lymph nodes (23). As has been shown, the pigment contains no iron, shows no bile pigment, is never crystalline and is insoluble in acid and alkalis (24). In a splendid scientific dissertation on the Dopa reaction, Laidlaw (25) mentions that the test is specific for two kinds of cells, the melanoblast, a term including all melanin producing cells as distinguished from mere phagocytes, and a myelogenous leukocyte which has no connection with melanin production. Both have a ferment, an oxidase, which converts dopa into melanin. Blackening of the cell is called the dopa reaction. Study of a rectum and colon with diffuse melanosis, which was removed surgically, showed that the pigment cells were dopa negative; therefore, he concluded that there are no melanoblasts and no melanin in the colon, or in the rectum above the anorectal line. Boyd reasons as follows, "the pigmented cells are dopa-negative and are, therefore, melanophores that have taken up the pigment which has either been ingested in the food or synthesized in the bowel.

So far as the pigmentation of the mucosa is concerned, no symptoms are cited. Invariably the patient will mention a habitual constipation and the use of various laxatives, but upon questioning, after visualization of the melanosis through the proctoscope, he

will usually admit the prolonged use of cascara or one of the other cathartics.

Of the twelve cases observed, eight had taken cascara frequently and other laxatives, only one was quite emphatic that none of the group had been used. The ages of the patients ranged between 30 and 66. One was a colored male; all the others were white. There were six males and six females. In one case, a man of 66 years of age, the condition was associated with diverticulosis of the sigmoid.

There is little to be said so far as the treatment is concerned, except the withdrawal of anthracene cathartics and correction of the constipation usually will

be rewarded by disappearance of the pigmentation. It has been estimated that three to six months is required. This is approximately the period observed in our cases.

SUMMARY

Twelve cases of Melanosis Proctocoli have been reported. While the condition is relatively uncommon, it is by no means as infrequent as usually considered. The fact that it only can be visualized by sigmoidoscopy, again emphasizes the importance of a complete examination of the rectum and sigmoid in all cases coming under observation.

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Carcinoma of Head of Pancreas Without Jaundice

By

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THE most common symptom of an advanced carcinoma of the head of the pancreas is a deepening jaundice. The carcinoma encroaches upon the common bile duct at its entrance into the duodenum damming back the bile into the biliary system and causing jaundice. It is safe to say that a diagnosis of carcinoma of the head of the pancreas would not be made unless the patient were jaundiced.

Thus it seems that the following case report of a carcinoma of the head of the pancreas without jaundice may be of interest.

CASE REPORT

M. W., 50 years of age, white, male, was first seen by me October 12, 1934. According to the patient's history he had been in good health until nine months previously. At that time he first noticed some discomfort in the upper abdomen which tended to come on after meals and which was not relieved by food. During these nine months the patient had had several attacks of nausea and vomiting. In spite of advice from his physician he had refused any satisfactory study of the gastro-intestinal tract.

About ten days before I first saw the patient, nausea and vomiting had become severe. The discomfort in the epigastrium became a constant pain. He was obliged to remain in bed. He could eat no solid foods and took only milk and cream.

At the time of my examination he was in acute distress.

During the half hour which I spent with him he vomited more than two quarts of dark green fluid.

Temperature was normal; pulse, 100 per minute. The tongue was dry and coated. The abdomen was markedly distended, especially across the epigastrium. There was no tenderness. No mass could be felt in the abdomen. No intestinal sounds were heard. Rectal examination showed no abnormality.

And there was no jaundice.

I made a diagnosis of pyloric obstruction.

The patient's stomach was drained by means of a Wangenstein tube. He was given large doses of 5% glucose intravenously and under the skin. He gradually improved.

A gastro-intestinal X-ray series was made. Films of the stomach and duodenum showed (1) a very large stomach; (2) a somewhat irregular pyloric ring; (3) considerable increase over the normal emptying time of the stomach; (4) a large six hour residue.

When the patient's general condition had improved as much as possible under the treatment outlined above, I operated. At operation I found the glands along the greater and lesser curvatures of the stomach and along the vertebral column markedly enlarged and stony hard; they were obviously involved in a neoplastic process. The head of the pancreas was also enlarged and stony hard. It was impossible to ascertain definitely where the neoplastic process had originated. The growth was pressing upon the duodenum in such a way as to cause a partial obstruction. I did a posterior gastro-enterostomy and re-

moved a lymph node which microscopically showed a metastatic carcinoma.

After operation progress was not satisfactory. X-ray treatments were tried but they caused marked nausea and vomiting and had to be discontinued. However, after some days the patient was able to be out of bed and was even able to shave himself.

During the next six weeks the patient grew steadily weaker, and he died January 1, 1935.

An autopsy showed that the original neoplasm had been in the head of the pancreas. It had encroached upon the duodenum and had caused an almost complete duodenal obstruction. It had also caused a complete obstruction of the common bile duct.

The fact that there had been no jaundice was explained as follows: at some time previous to his last illness, the patient had had a gall stone in the gall bladder. The stone had ulcerated into the duodenum and had established a sinus between the gall bladder and the duodenum. Bile

had drained through this sinus into the gastro-intestinal tract and was not dependent for a passageway on the common bile duct which was now occluded by the neoplasm. It had flowed freely into the duodenum distal to the obstruction. Thus, a simple mechanical readjustment by Nature explains the phenomena of a Carcinoma of the Head of the Pancreas without Jaundice.

SUMMARY

A patient with a very extensive and advanced carcinoma of the head of the pancreas, which was proved by operation and autopsy, did not develop jaundice. Failure to develop jaundice was explained by the fact that at some previous time a sinus had formed between the gall bladder and the duodenum, thus allowing free drainage of the gall bladder into the duodenum, independently of the common bile duct which had been occluded by a carcinoma.

Calcium Gluconate and Kaolin in the Treatment of Bacillary Dysentery*

By

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OVER 1,000 cases of bacillary dysentery of Flexner type have been observed and treated by the authors in the past two and one-half years. In a small percentage the acute phase became chronic, indistinguishable clinically and proctoscopically from chronic ulcerative colitis, and as a rule persisted in spite of various treatments. In June, 1937, we decided to use the Haskell and Cantarow (1) method of calcium, kaolin and parathyroid extract treatment, first reported in 1931. However, before we were able to begin this study, our chronic cases had dwindled to two. We then proceeded to use this method in acute cases, modifying it by omitting belladonna and using our regular soft diet.

Since the patients under discussion are psychotic, it is usually impossible to obtain subjective information concerning the efficacy of treatment, and all conclusions were necessarily based upon objective findings. Fortunately, we had previously performed about four thousand proctoscopic examinations upon dysenteric cases and had observed the mucous membrane of the lower twenty-five centimeters of the large bowel in all phases of the disease. One of us, (L. H. B.) (2), had reported in a previous article that the infection apparently starts in the terminal ileum or cecum and travels downward, whereas when healing takes place it starts at the muco-cutaneous junction and always travels cephalad. Furthermore, the mucosal picture invariably corresponds to the clinical picture, i.e. the more severe the infection, the more marked the mucosal change. We have graded the proctoscopic mucosal picture into four groups: One plus (+) where there is a mild hyperemia and no blood vessels visible; two plus (++) where there is a moderate

hyperemia; three plus (+++) where there is an intense hyperemia and edema; and four plus (+++++) where the mucosa is intensely hyperemic, edematous and ulcerated. Healing, when it took place, always was a reverse of this order of involvement. A method was thus afforded to evaluate our results objectively according to the above groupings.

TABLE I

Relation of calcium given to average duration of hospitalization

Mucosal Appearance	Number of cases receiving Calcium in indicated amounts				Average days of morbidity
	10% once daily	20% once daily	10% B.I.D.	20% B.I.D.	
Moderate ++	3	2	3		6
					6
				4	5
					4
Intense +++	5	5	5		15
					13
				4	9
					7
Ulcerated +++++	4	3	3		25
					14
					21
				3	15

*From the Department of Proctology, service of Dr. L. H. Block, Elgin State Hospital.

MODE OF ACTION

In developing the logic for the combined calcium and kaolin method of treatment used in this study it is best perhaps to consider certain aspects of bacillary dysentery in conjunction with the physiologic and

TABLE II

Comparison of the mortality and morbidity in the calcium and calcium-parathyroid groups

Mucosal Appearance	Calcium Group Cases	Calcium Parathyroid Group Cases	Morbidity	Mortality
Moderate ++	12		8	0
		5	6	0
Intense +++	22		11	3
		1	24	0
Ulcerated ++++	15		19	0
		7	17	1

pharmacologic properties of the medicaments used. In the first place this disease is extremely debilitating and the patient suffers not only from toxemia, but from dehydration due to profuse bloody and mucous diarrhea as well. There is a diffuse inflammation of the colon that ultimately leads to necrosis and ulceration. The intestinal ulceration is so important that much study has been devoted to the mechanism of its production. Thus experimental and clinical evidence suggests that the primary intestinal lesions are due to a necrosing action of a thermostabile endotoxin, which after passing through the liver, is excreted from the blood vessels through the wall of the bowel into the lumen. Flexner (3) in 1906 first called attention to toxin excretion rather than the local action of the organism itself as the cause of ulcers.

An excess of calcium intake above the minimum required for the maintenance of physiologic function according to Sherman (4), Bernheim (5) and others makes the difference between a passable and buoyant state of health. Naturally, in the treatment of dysentery an improved state of health in the patient is of the greatest importance and for this general purpose alone calcium therapy is well justified. In addition, it alleviates symptoms of dysentery, promotes the healing of intestinal lesions and hastens the recovery of the

TABLE III

Analysis of mortality according to age group

AGE Years	CONTROL		CALCIUM	
	Cases	Deaths	Cases	Deaths
20 - 39	20	0	23	1
40 - 59	35	11	27	3
60 - 80	20	7	10	0

Comparison in Mortality between the Calcium and Control Groups

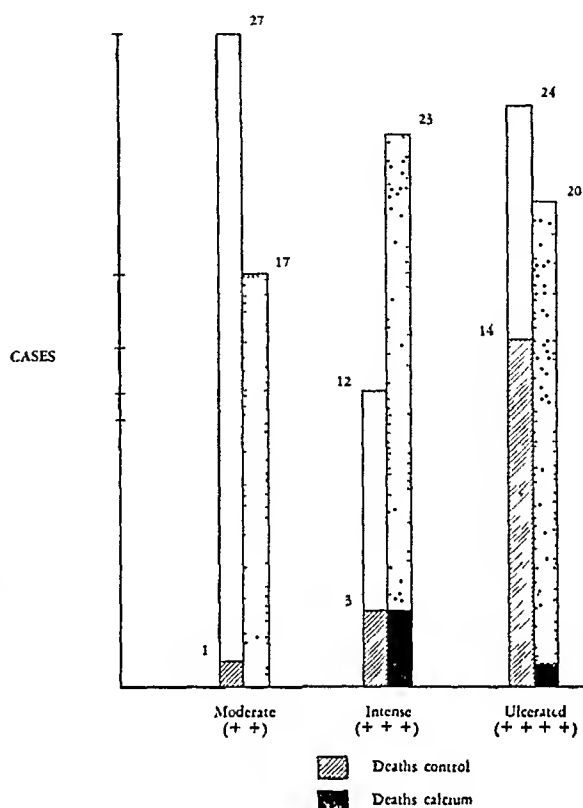
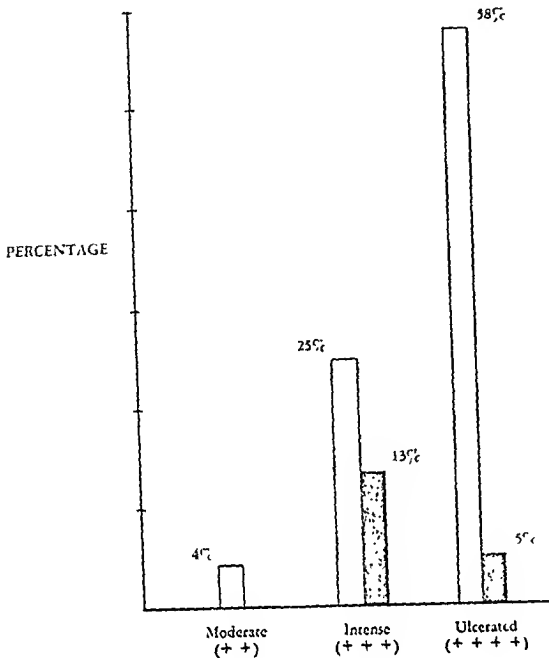


Fig. 4

patient. By its sedative action calcium tends to allay the irritated state of the colon; further, it increases the resistance of cells to permeation by blood and lymph and thus helps to control bleeding from the ulcerated mucosa and prevents dehydration by reducing the exudation and transudation into the colon; calcium also stimulates immune processes of the body, protects liver tissue and function in toxic states, and is an antidote to toxic products, such as guanidine, generated as a result of tissue injury. The influence of intensive calcium therapy in overcoming allergic reactions has received much comment in the literature by various investigators and recently Silverman (6) has reported certain cases of bacillary dysentery that presented symptoms due to specific protein hypersensitiveness. Thus calcium has a number of physiologic and pharmacologic properties and the combined effect of some, if not all, of these apparently accounts for the benefit derived from calcium therapy in dysentery.

The literature dealing with diseases of the intestinal tract reveals the beneficial use of kaolin (China clay, bolus alba, purified aluminum silicate). Kaolin has been successfully used for centuries in the Orient. It was however, during the Balkan epidemic of cholera in the Balkan War in 1913, that Stump's bolus treatment (bolus alba) was tried at Nish by Kulme with remarkable results. Later, Walker (7) and Braasfladt (8) in 1919 used it extensively in the dysenteries in China. Kaolin is an inert powder possessing tre-

Comparison of Mortality between the Control and Calcium Groups According to Severity of the Infection



Shaded columns represent Calcium Group

Fig 5

showed some beneficial effect over the same period of time. However, the patients receiving the combination by mouth showed a higher percentage of improvement. The next procedure included oral calcium and kaolin plus intravenous or intramuscular injections of calcium glucono-galactogluconate* in 10% and 20% concentrations which are made possible by the high degree of solubility of this new salt.

Fig. 1 showed the marked decrease in the average morbidity when the calcium injected was given in 20 per cent solution, twice daily.

The last procedure consisted in the oral administration of calcium and kaolin, plus injections of calcium complemented by subcutaneous injections of parathyroid extract in a group of thirteen cases. Although the results were somewhat better than in the fourth procedure, (see Fig. 2) the added cost in our opinion did not justify its use in the remaining cases.

The dosage we are now using and the one that is giving us the best results is the intravenous or intramuscular injection of 10 cc. of 20 per cent calcium glucono-galactogluconate twice daily, complemented by two drams each of kaolin and calcium gluconate with or without an equal amount of Cal-C-Malt given every two hours orally.

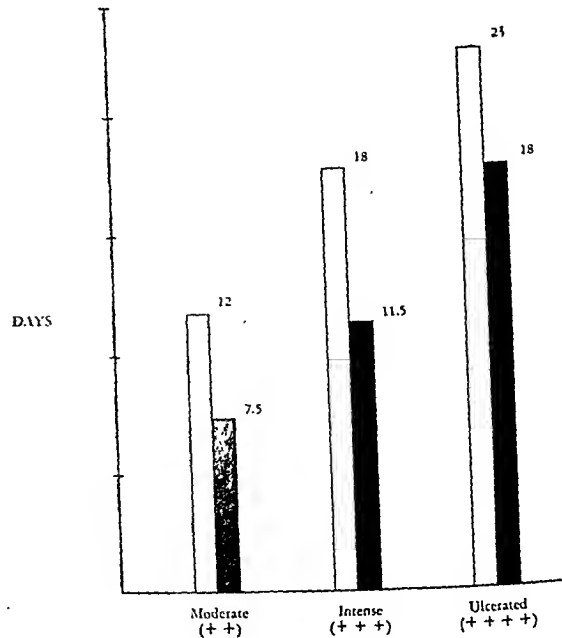
RESULTS

From the months of July to October, 1937, we had 135 cases of acute bacillary dysentery. Seventy-five of these were used as a control and received no medication whatsoever, whereas 60 received calcium in various combinations.

An analysis of our cases revealed a great disparity

*Neo-Calglucon supplied through courtesy of Sandoz Chemical Company.

Comparison of Morbidity in the Calcium and Control Groups



Shaded columns represent the Calcium Cases

Fig. 6

mendous surface area and high adsorptive ability. Braasfladt (8), in a comprehensive study of the effect of kaolin on the intestinal flora in normal and pathological conditions, concluded that it carries down large numbers of bacteria from fluid media, if kept in motion; and it neutralizes various pathologic bacterial toxins; that when administered orally over a period of ten to thirty days in daily doses of one to two ounces, it changes the intestinal flora of human beings from a predominantly proteolytic to an aciduric type; (incidentally an editorial, J. A. M. A., November 13, 1937, commented upon the recent study of Eppwright, Valley and Smith, who showed the value of calcium and phosphorous in producing an increase in aciduric organisms). Walker (7) in discussing the rationale of kaolin concluded that its action is twofold: mechanical, by forming an adherent coating to the wall of the bowel, and by enclosing and carrying with it a very large number of bacilli; and, adsorptive, by adsorbing toxins. He further states that the layers of this inert substance on the walls of the intestinal tract act as a filter bed against effete material.

ADMINISTRATION

Our method of administration and the best combination of calcium and kaolin was arrived at by trial and error. First, calcium and kaolin were given separately, and then in combination. At the end of one week's observation, only one patient out of the ten that received calcium orally showed any improvement, whereas two out of ten that received kaolin by mouth

in the mortality of the two groups. The control group showed a mortality of twenty-four per cent as compared with seven per cent in the group treated with calcium.

We have analyzed our results according to the severity of the infection, believing that by doing so, we should have a better comparison. Fig. 4 compares the mortality as to severity of the disease, giving the number of cases in each grouping. Fig. 5 gives the percentage of deaths in each grouping. It will be noted that the death rate decreased 50 per cent by the use of calcium in the "intense" (+++) group, while in the ulcerated (++++) group, the mortality was 58 per cent, as compared with 5 per cent in the calcium group. An analysis of the deaths according to age groups further showed that the decrease was more marked in the 60 to 80 year group (see Fig. 3). An interesting observation was the decrease in the morbidity (the average number of days of hospitalization) of patients receiving calcium (see Fig. 6). The more rational patients stated there was a marked recession of abdominal cramps as soon as the intravenous injection was given. Some complained of a sensation of intense body heat following the injection. Over 900 injections of calcium were given without any local reaction or pain.

CONCLUSIONS

1. In sixty cases of bacillary dysentery the combined calcium and kaolin method of treatment herein described reduced the mortality by 50% to 75% depending upon the severity of the infection.

2. The period of hospitalization was reduced, but not notably.

3. The best results were obtained with intravenous or intramuscular injections of calcium gluconate supplemented by oral dosage with calcium gluconate and kaolin.

4. Parathyroid extract has but slight value in the intensification of calcium effects and its high cost does not warrant its use.

5. While the detailed action of the calcium and kaolin treatment used cannot be wholly explained, nevertheless, it seems entirely logical that the beneficial effects obtained are due to a combination of several well known properties of both substances.

6. Combined treatment with calcium and kaolin is more satisfactory than therapy with either of these medicaments used alone.

7. The above described therapeutic method is not offered as a specific but as a valuable adjunct to other proved medical measures.

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Human Autonomic Pharmacology

XVII. The Effect of Acetyl-Beta-Methylcholine Chloride on the Gall Bladder*

By

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ACETYL-BETA-METHYLCHOLINE chloride (mecholy) is a choline compound closely related to acetylcholine. In physiologic research and in therapeutics, it has to a large extent replaced this latter drug because it is more nearly a total parasympathetic stimulant. While the general effects of acetylcholine include a parasympathetic effect with the inhibition of cardiac action and an increase of intestinal tonus, a vasodilating action, and a nicotine-like effect causing a rise in blood pressure when the other actions have been abolished, acetyl-beta-methylcholine, although it is a parasympathetic stimulant and causes a dilatation

of the peripheral blood vessels, has no nicotine-like effect. The general physiologic actions of acetyl-beta-methylcholine are (a) marked flushing of the skin extending over the face, chest, and upper part of the abdomen; (b) increased pulse rate; (c) a deeper and slower respiratory cycle; (d) a marked drop in blood pressure; (e) marked salivation; (f) marked lacrimation; (g) profuse alkaline diaphoresis; (h) slight cyanosis at the tips of the extremities with a drop in the surface temperature; (i) diuresis in certain persons; (j) occasional substernal pressure; (k) changes in electrocardiogram with temporary inversion of T waves in one or more leads; (l) increased intestinal tonus, peristalsis, and defecation rate. To

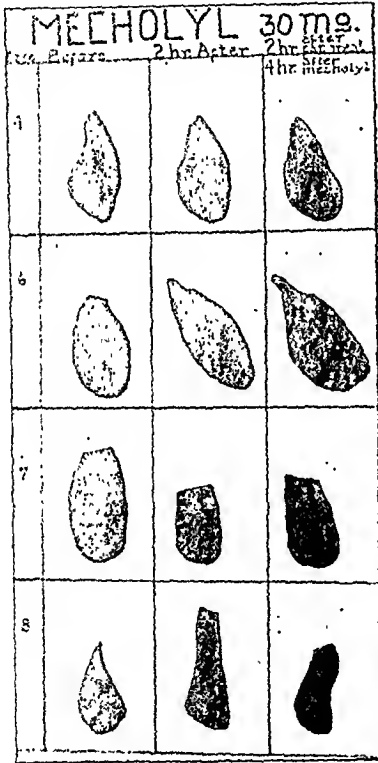
*From the Research Division of the Boston State Hospital, Boston, Mass., aided by grants from the Commonwealth of Massachusetts, The Rockefeller Foundation, and the Milton Fund.

the best of our knowledge there are no studies upon the effect of this drug upon this viscus. It is the purpose of this paper to present such a study.

METHOD

The patients in this study were all mentally ill but physically normal. All of them were males with an age range of from 22 to 40 years. Each patient was used as a control on himself and on the entire group.

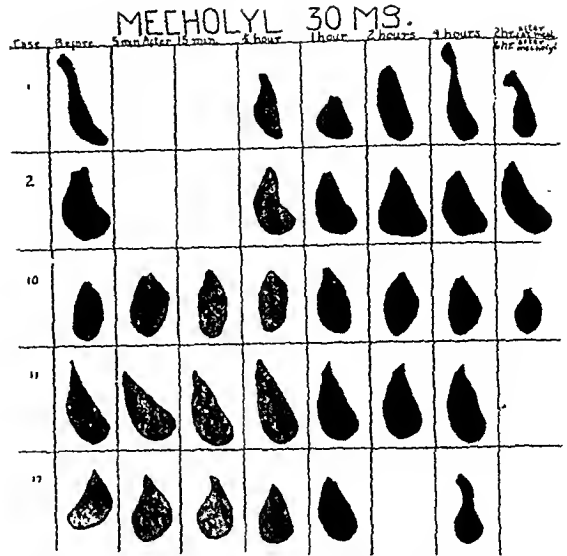
Control Study. Before the drug study was started, each patient was given a gall bladder dye test to determine the size and rate of emptying of the gall bladder. The night before the test the patient received a light meal, which consisted of dry toast, tea and sugar. One hour later he was given the gall bladder dye, tetraiodo-phenolphthalein sodium orally. The following morning after a fast of at least 15 hours, X-ray films were taken of the gall bladder region. He was then given a meal rich in fat, which con-



sisted of two slices of white bread thickly spread with butter, and two glasses of a milk and cream mixture into which had been beaten four raw eggs. After lapses of from 1 to 2 hours, X-ray films were again taken. Only those individuals were used in whom there was either a marked diminution or complete absence of the gall bladder shadow on the X-ray films that had been taken after the fatty meal. This method of dye administration and type of meal were used throughout the work.

Acetyl-beta-methylcholine study. Group 1. In this series the patient was given 30 mg. of meeholyl subcutaneously after the initial X-ray films of the dye-filled gall bladder had been taken. Two hours after the administration of the drug films were again taken, and the patient was immediately given the fatty meal. The films were again repeated two hours later.

Group 2. In this series after initial X-ray films had been taken, the patient was given 30 mg. of meeholyl subcutaneously, and subsequent X-ray studies were made



5, 15 and 30 minutes, 1, 2 and 4 hours after the drug had been administered. Each patient was then given the fatty meal and the films repeated in 2 hours.

RESULTS

Charts 1 and 2 are tracings of gall bladder shadows as visualized on the X-ray films of the patients in Groups 1 and 2 respectively.

Group 1. The effect of meeholyl on the dye-filled gall bladder was studied in these patients before the administration of the fatty meal. The X-ray films that were taken 2 hours after the drug had been given show little, if any, change in the size of the gall bladder shadow. In Cases 6 and 8 there was a slight increase and in Case 7 a decrease in the size of the shadow. The fatty meal was given to the patients and subsequent films, taken two hours later, showed a gall bladder shadow in every instance. In Case 6 the gall bladder shadow had increased in size.

Group 2. In this series of cases the effect of meeholyl on the dye-filled gall bladder was studied at frequent intervals over a 4 hour period before the administration of the fatty meal. These films, taken at 5, 15 and 30 minutes, 1, 2 and 4 hour intervals after the administration of the drug, showed no important changes in the size of the gall bladder shadows. The fatty meal was given to each patient 4 hours after the drug had been administered, and subsequent films showed an absence of the gall bladder shadow in only two cases.

DISCUSSION

The motor innervation of the gall bladder is unquestionably autonomic. Mann (1) in 1924 after reviewing the older literature concluded that the parasympathetic and sympathetic nerves to the gall bladder each carry both motor and inhibitory fibers, but that the parasympathetic was predominantly motor and the sympathetic inhibitory. More recent literature (2, 3, 4, 5, 6) on the cat and dog indicates that parasympathetic stimulation has little effect on the gall bladder as measured by evacuation. Whitaker (5) filled the gall bladder of the dog and cat with iodized oil and stimulated one vagus in the neck centrally and peripherally after recovery from anes-

thesia without observing evacuation. The animals evacuated later after a fat meal. Crandall (3) using the same method, stimulated the vagus just above the diaphragm and failed to obtain emptying. The gall bladder evacuated after a fat meal. Ivy (7) who has made many observations on the physiology of the gall bladder supports the conclusions of Mann. Westphal (8), using the guinea pig, found that weak stimulation of the vagus produced contraction and evacuation of the gall bladder and that this response was augmented by previous splanchnic section. Section of the vagus was without much effect. Splanchnic stimulation caused a relaxation of the gall bladder. When both vagi and the sympathetic nerves were sectioned, the motility was normal. On the other hand Dubois and Kistler (9) and Burget and Brocklehurst (10), failed to obtain evacuation of the gall bladder of the guinea pig after vagus stimulation. Ivy (7) states that in addition to the autonomic innervation of the gall bladder described there must exist for proper emptying a reciprocal innervation between the gall bladder and the sphincter of Oddi, i.e., when the gall bladder contracts, the sphincter of Oddi must relax. A large amount of experimental work which would tend to establish such innervation has been evaluated by him.

It would appear that the bulk of the experimental work on the motor innervation of the gall bladder indicates that parasympathetic stimulation does not produce an evacuation of the gall bladder. This being so it might be anticipated that mecholyl, a parasympathetic stimulant, would not produce an evacuation of the gall bladder. Such an anticipation would be strengthened by work with acetyl choline. The isolated gall bladder of dogs and guinea pigs has been observed to contract quickly and markedly following the application of this drug (11, 12, 13). Wood (14), using biliary fistula dogs has observed a flow of dark bile after the injection of acetyl choline, but when he placed a balloon in the gall bladder, he failed to obtain evidence of contraction. Voegtlin and Ivy (15), could obtain no evidence of contraction in the dogs' gall bladders after the injection of acetyl choline.

In our work the above expectation and the work on acetyl choline was further substantiated. As has been shown, in no instance did the gall bladder empty following the administration of acetyl-beta-methylcholine chloride (mecholyl). In addition to this mecholyl apparently delayed the emptying of the gall bladder after a fat meal. This delay was definite and observed in a sufficient number of cases to eliminate chance occurrence. In control studies performed upon the same patients no such delay was observed. Such an observation can mean only one thing, i.e., that mecholyl in addition to acting as a parasympathetic stimulant on the gall bladder per se also sets in motion another series of events which makes the gall bladder incapable of emptying after the administration of a fat meal. The actual mechanisms producing such inhibition are at the present unknown.

Ivy (7), in an attempt to evaluate the various factors concerned in gall bladder evacuation states: "In the relatively rapid type of evacuation of the gall bladder of man and dog, which occurs after the ingestion of a meal of egg yolk and cream, or fat, the evidence shows that the chief factor concerned is a

rise in intra-gall bladder pressure. This rise is due primarily to a more or less sustained tonic contraction of the musculature. The contraction is excited in part by a hormone (cholecystokinin) and by reflex nervous mechanism (cephalic and gastro-intestinal). The sphincter of Oddi and the duodenal musculature promote evacuation by relaxing and permitting bile to be expelled by the contracting gall bladder. The evidence shows that reciprocal functional relationship exists between the gall bladder and choledochoduodenal mechanism; but whether this relationship is causal is an open question. The evidence also shows that duodenal peristalses are not essential for, but assist evacuation. Peristalses may act by exerting a milking action on the intramural portion of the common duct. There probably exists some unknown intrinsic correlation between the sphincter of Oddi and the duodenal musculature, so that when the duodenum relaxes before an advancing wave of contraction, the sphincter relaxes. The evidence indicates that elastic recoil, attributable to both the elastic and muscular tunie of the gall bladder, may in the presence of 'high' intragall bladder pressure and a decrease in intramural resistance cause some evacuation. The dilution of bladder bile by hepatic bile, as determined by changing intramural resistance, the secretory pressure of the liver, and the phases of gall bladder contraction are concerned in the final or complete renewal of the contents of the gall bladder, or in the complete disappearance of the cholecystographic shadow."

In addition to this there exists a pertinent literature on the relationship of gastric acidity (16, 17, 18, 19, 20) to gall bladder evacuation and mobility (21, 22, 23, 24, 25, 26) which cannot be ignored. In this respect it has been demonstrated by us (27) that mecholyl definitely increases gastro-intestinal tone. Whether one of these factors is in any way responsible for the phenomena observed in the gall bladder or whether they are all the result of some fundamental chemical change such as is being observed in this laboratory in the tissue esterases is unknown. In any attempt to explain the inhibiting effect which mecholyl has upon the evacuation of the gall bladder all of these factors must be taken into consideration. In this paper this is quite impossible and impracticable, and we prefer to await the results of further studies which we have in progress to assist us in this respect.

Clinically, however, this work would seem to indicate that (a) there is no contraindication to the use of mecholyl in spastic gall bladder disease or in cholelithiasis; (b) mecholyl cannot be given to individuals who are having roentgenological gall bladder studies to determine the normal rate of emptying; and (c) emptying of the gall bladder by a fat meal can be prevented by the administration of mecholyl.

SUMMARY

A study of the effect of acetyl-beta-methylcholine chloride (mecholyl) on the gall bladder is presented.

It has been demonstrated that mecholyl has practically no effect upon the size and shape of the gall bladder, but that this drug in the majority of cases very definitely inhibits the emptying of the gall bladder following the ingestion of a fat meal.

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Digestion and Absorption in a Man With Three Feet of Small Intestine

By

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DURING the summer of 1935 the writers had the unusual opportunity of studying digestion and absorption in a patient† of the U. S. Veterans Hospital, who, as a result of five resections at intervals over a period of eleven years, retained some three feet of small intestine (34 inches according to the surgeon's measurements). Less than a foot of jejunum remained. The last resection was done in 1933. He was operated on for intestinal obstruction in 1930 and 1933. Shortly after the latter operation severe diarrhea and tetany supervened necessitating calcium and Vitamine D therapy. An exploratory laparotomy was performed in March, 1935, and the small intestine found to be dilated and hypertrophied almost to the size of a normal large intestine. The lacteals showed unusually distinctly. The ileocecal valve appeared normal. There were some soft enlarged glands about 8 inches above it. There were relatively few adhesions and the entire intestinal tract appeared relatively free from disease with the exception of the dilatation and hypertrophy of the small intestine which the surgeon considered to be compensatory to its shortness.

When the patient came to the attention of one of us (M) March 30, 1935, he appeared as a fairly well developed man of 40 years, 5 feet 8 inches tall, in poor nutrition, and moderately cyanotic. The most note-

worthy symptoms were those associated with tetany. All reflexes were greatly exaggerated. The abdomen was quite uniformly distended and tympanitic.

TABLE I
Blood Ca and P on subject H

Date	Mg. Ca	Mg. P	Remarks
4-5-'35	6.5	—	In typical tetany.
4-10-'35	5.6	4.0	45 grains Ca gluconate + 5 minims viosterol t. i. d. beginning 4-11-'35.
4-16-'35	6.2	—	
4-17-'35	6.1	3.3	
4-24-'35	6.9	3.1	90 grains Ca gluconate beginning 4-20-'35.
5-8-'35	6.5	3.7	135 grains Ca gluconate 5-2-'35. Increased to 165 grains 5-9-'35.
5-15-'35	7.0	—	
5-27-'35	6.9	—	Viosterol increased to 10 minims t. i. d. 5-27-'35.
6-4-'35	8.7	—	
6-12-'35	7.6	—	
6-20-'35	8.0	—	Discharged from hospital 6-25-'35. Tetany relieved.
8-1-'35	9.2	—	Able to do light work.
10-12-'35	9.2	—	

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†The patient apparently suffered from regional ileitis.

TABLE II
Daily intake of foods by subject H in grams

Date	Carb.	Prot.	Fat	Ca	P	Calories*
6-18-'35	253	128	136	2.80	2.23	2748
6-19-'35	287	134	219	2.62	2.06	3655
6-20-'35	234	103	156	2.26	1.82	2752
6-21-'35	261	101	190	2.71	2.07	3158
5-22-'35	359	133	157	2.76	2.05	3381
6-23-'35	189	214	172	2.55	2.79	3160
6-24-'35	268	119	151	2.77	2.26	2907
Total	1851	932	1181	18.47	15.33	21761
Average	254	133	169	2.64	2.19	3109

*Calculated on the basis of 4 Cals. per gm. for carbohydrate and protein and 9 Cals. per gm. for fat.

The treatment given was designed to combat tetany and consisted in the oral administration of calcium gluconate and Vitamine D (viosterol). Table I gives data relative to blood Ca and P of the patient during the period of observation.

The patient was exceedingly temperamental and insisted upon choosing his foods "a la carte" and it was only upon agreeing to let him do this that he agreed

calcium, and phosphorous contents for each meal were calculated from tables of food values. The patient received 165 grains of calcium gluconate daily during the experimental period. The calcium equivalent of this was added to the food calcium in calculating the total calcium intake. The stools, which were frequent and copious, were collected, mixed with sulphuric acid, and made to constant volume for analysis. Urines

TABLE III
Excretions by subject H in grams

Date	N		Carb. Feces	Fat Feces	Ca		P		Feces Ca Feces Fat
	Urine	Feces			Urine	Feces	Urine	Feces	
6-18-'35	9.3	5.05	1.96	78	0.009	2.11	0.436	1.33	0.027
6-19-'35	16.2	5.24	1.55	80	.002	2.03	.673	1.36	.025
6-20-'35	12.9	8.35	3.33	126	.001	3.79	.539	2.13	.030
6-21-'35	12.8	2.45	0.74	34	.006	0.90	.547	0.68	.026
6-22-'35	19.9	7.34	2.80	98	.009	2.97	.399	1.88	.030
6-23-'35	19.2	4.02	1.49	66	.008	1.51	.543	1.20	.023
6-24-'35	13.5	3.72	1.72	49	.006	1.47	.448	0.92	.030
Total	103.8	36.17	13.59	531	0.041	14.78	3.58	9.50	
Average	14.97	5.17	1.94	76	0.006	2.11	0.51	1.36	0.023

to serve as an experimental subject. Consequently, it was impossible to place him upon an accurately analyzed diet. Through the cooperation of the Hospital Dietician he was permitted to select his foods for each meal, which were then weighed and served. A representative dietary is shown in Table V. It contained very little non-utilizable carbohydrate. The subject ate four meals per day. The carbohydrate, protein, fat,

were preserved with toluene. The experimental period included seven consecutive days, June 17 to 24. The patient's weight increased from 130 to 131 pounds during the experimental period.

METHODS OF ANALYSIS

Urine and feces were digested according to Gerritz (1). Fecal calcium was determined in the digest by

TABLE IV
Summary of food intake and excretion by H in grams for seven day period

	Carb.	Prot.	Fat	Ca	P	Cal.
Intake	1851	932	1181	18.47	15.33	21761
Loss by excretion	13.6	226	531	14.52	13.03	5737
Difference	1837.4	706	650	3.65	2.25	16024
Per cent used	99.3	75.8	55.1	19.8	14.7	73.6

TABLE V
Representative dietary of subject H

Breakfast		Lunch		Dinner		Supper	
Cantaloupe	150 gm.	Creamed Tomato Soup	100 gm.	Cream Clam Soup	200 gm.	Bread	25 gm.
Bread	75	Veal Cutlets	100	Beef Stew	100	Beef	25
Milk	200	Escalloped Potatoes	100	Potato	100	Milk	500
Cream	150	Tomatoes	100	Pineapple	50	Chocolate Creams	45
Eggs (2)		Apple Pie	100	Cottage Cheese	25		
Ham	100	Iced Tea with sugar	6	Cantaloupe	150		
		Cheese	10				

This dietary was calculated as equivalent to about 268 gm. carbohydrate, 119 gm. protein and 151 gm. fat with a caloric value of 2207 calories.

the method of Shoal and Pedley (2) and urine calcium by the method of Kramer-Tisdall as modified by Clark-Collip (3). Fecal and urine phosphorous were determined in the digests by the Briggs' modification of the Bell-Doisy method (4). Nitrogen of feces and urine was determined by the Kjeldahl method and converted to protein equivalent in the usual way. The carbohydrate of feces was determined by hydrolyzing with 1 N H_2SO_4 (gently boiled under reflux for 5 hours), followed by defecation of the hydrolysate with $HgSO_4$ — $Fe_2(SO_4)_3$ — $BaCO_3$ (5), and estimation of the fermentable sugar in the filtrate using washed yeast and the Shaffer-Somogyi reagent No. 50 (6). Fermentable urine sugar was determined but the quantity was negligible. Total fat in the feces was estimated by the method of Saxon (7). The proportion of fatty acids to total fat was determined on three unpreserved fresh samples of feces and found to be 85, 81 and 86 per cent calculated as stearic acid.

Data obtained relative to food intake, excretion and balance are summarized in Tables II-IV. The figures of Table IV show that carbohydrate was excellently utilized, undoubtedly as well as by the normal individual. About 25 per cent of the protein was lost in the feces and 45 per cent of the fat. The fat excreted was, however, rather well digested since better than 80 per cent of the total fecal fat was found present as free fatty acids (calculated as stearic). This excessive excretion of fatty acids was undoubtedly in great part responsible for the large loss of Ca in the feces (as calcium soaps). In Table III the ratio of fecal Ca to fecal fat is seen to be remarkably constant for this type of experiment. Table II shows that the average daily intake of carbohydrate, protein, and fat was 265, 133, 169 grams respectively with a caloric value of 3109 Cals. Of this, on the average, he utilized about 262 grams of carbohydrate, 93 grams of protein, and 101 grams of fat with a total caloric value of 2287 Cals. He lost roughly 25 per cent of the caloric value of his food. Table I shows a progressive improvement in the blood calcium of the subject as a result of large doses of calcium gluconate and viosterol. During the period of the metabolism study he was in positive calcium and phosphorus balance and his blood calcium,

though somewhat low, was definitely improved. Undoubtedly a diet containing relatively more carbohydrate and less fat would have been advisable for the subject in promoting calcium absorption, but his personal likes and dislikes prevented this being tried.

The efficiency of the intestine in digesting and absorbing food materials is strikingly brought out in this subject with only 12-15 per cent of the normal length of small intestine remaining. To be sure the absorbing area of the intestine was greater than 12-15 per cent of normal because of hypertrophy, yet the food remained in contact with the absorbing surface for a much shorter time than normal because of the diarrheal condition. Apparently nature has indeed provided the human with a safe excess of small intestine. Fat absorption would appear to be the chief limiting factor necessitating anything like the normal length of small gut.

SUMMARY

Digestion and absorption in a man with three feet of small intestine has been studied over a seven day period.

The assimilation of carbohydrate was found to be normal.

About 25 per cent of the ingested protein and 45 per cent of the fat was lost in the feces representing roughly 25 per cent of the caloric value of the ingested food. The fecal fat contained a large proportion of free fatty acids indicating fairly satisfactory digestion of fat and poor absorption of fatty acids.

A high calcium and viosterol intake was necessary to keep the man in positive calcium balance. The large amount of fatty acids in the feces was probably chiefly responsible for the poor calcium absorption. The daily ratio of fecal calcium to fecal fat was remarkably constant which tends to support such an explanation.

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ADDENDA: The man has just been readmitted to the U. S. Veterans Hospital in a condition of tetany. Further studies are planned if possible.

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Melanosia Coli in a Boy Aged Two and One-Half Years*

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IN 1933 Bockus, Willard and Bank reviewed the literature on Melanosis Coli and presented a series of forty-one cases in which the use of anthracene laxatives (cascara, aloes, senna, rhubarb and frangula) apparently had some etiologic significance. Zobel and Susnow, 1935, reported seven cases of this condition in patients using anthracene laxatives. The following case report is of interest in this connection.

CASE REPORT

R. L., male, age two years and six months, was first seen on May 3, 1937. His mother stated that constipation had been a problem since birth. The birth weight was 8 pounds, 13½ ounces. Development had been normal. Breast feeding was stopped after three months, the artificial feedings being reinforced with fruit juices and cod liver oil. Vegetables were added at seven months. Because of constipation various lubricants and mild laxatives were used from time to time and enemas frequently were required. In November, 1936, Fluid Extract Cascara Sagrada, 5 to 15 drops daily, was prescribed and gradually increased to 15 drops three times daily. In February, 1937, a mixture containing Fluid Extract Cascara Sagrada, Tincture Belladonna and Elixir Lactopepsin was substituted. The dosage prescribed amounted to 10 drops of the fluid extract of cascara three times daily; this was increased to the equivalent of 20 drops after a few days and was continued until admission. Enemas were given frequently. For six months this patient had received cascara almost daily.

Examination revealed a well developed white boy who appeared nervous and irritable. The general examination was not noteworthy. Rectal examination showed good sphincter tone, proctostasis, and a dilated rectum. By sigmoidoscopy, after a cleansing enema, the typical brown pigmentation of Melanosis Coli was seen. The color was medium dark brown and showed the irregular yellow striae described by previous writers as producing a "toads back" appearance. This condition extended at least six inches above the anus, the highest point reached with the sigmoidoscope.

Barium enema Roentgen studies demonstrated a colon of average size without defects.

Laboratory studies: Blood count: erythrocytes 3,870,000; leucocytes 6,200; neutrophils 55%; lymphocytes 39%; monocytes 6%; hemoglobin 78%. Urinalysis essen-

tially negative. Fecal analysis: undigested food in excess, fatty acids, faint trace occult blood.

On May 10, 1937, a program was outlined which included a bland diet, bland bulk (Mucilose), mineral oil, adequate vitamins, and an antispasmodic laxative powder containing extract of belladonna, magnesium oxide, calcium lactate and kaolin. The response was immediate and no further enemas or additional laxatives were given. Two weeks later (5/24/37) the sigmoidoscopic picture was practically the same as on the first examination, but in five weeks from the beginning of treatment (6/14/37) the pigmentation had disappeared entirely leaving only a mild congestion of the rectal mucosa. The patient's appetite and disposition had improved. Subsequent examinations (8/23/37 and 2/8/38) revealed a normal rectal mucosa.

DISCUSSION

The case here presented supports the view that the anthracene group of laxatives can produce Melanosis Coli. For six months this boy had been given laxatives of this type. There is no suggestion of the administration of heavy metals such as mercury or bismuth, which have been reported as causing pigmentation of the bowel, nor is there any evidence of intestinal bleeding. The appearance of the mucosa of the rectum through the sigmoidoscope was identical to that of the cases previously reported. Evidence of proctostasis was also present.

A survey of the literature reveals that the youngest previously reported case is that of Henschen and Bergstrand, a boy of thirteen years whose history is not recorded.

SUMMARY

A case of Melanosis Coli occurring in a boy aged two and one-half years is recorded. No report of this condition in a patient of this age can be found in the literature. The laxative history supports the premise of Bockus, Willard and Bank that the use of anthracene laxatives can produce a pigmentation of the bowel indistinguishable from Melanosis Coli.

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The Medical Treatment of Cholecystitis*

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THE frequency with which cholecystitis occurs and the serious character of its consequences merits the great attention which it has received.

This subject has already received so much attention from surgeons, pathologists, physiologists and clinicians that the vast accumulation of factual material is so great that evaluation and interpretation are difficult. This is true concerning experts in each domain of investigation.

TABLE I

In 1,650 cases presenting gastric symptoms, cause of dyspepsia was organic pathology of the gall bladder, in	52 per cent
Blackford and Dwyer (1)	
In 1,000 routine post mortem examinations, signs of chronic and healed cholecystitis in	300
Estimates 40 per cent of the adult population have disorders of the biliary system.	
Crump. (2)	
All laparotomies in one hospital, cholecystectomies	5 per cent

In recent years the preponderance of medical opinion, greatly influenced by surgeons and pathologists, has been increasingly in the direction of regarding the disease as surgical, maintaining that change in the gall bladder wall, with or without stones, is the essential lesion and that surgical removal of the gall bladder is the remedy of preference, more especially if stones are present. This opinion, however, is not accepted without some qualification.

One observer (3), calls attention to the fact that in about one-third of the operations for the relief of gall bladder disease no stones are found, and in 90 stoneless cases observed for three and one-half years after cholecystectomy, there was no improvement in 47 per cent of the cases.

Whipple (5) writes: "We believe that conservative therapy is preferable to surgery in the majority of cases of chronic cholecystitis unless there is positive evidence in the history of biliary colic and typical interval digestive disturbances, such as bloating and belching, plus corroborative X-ray evidence of gall stones, or nonvisualization of the gall bladder by cholecystography."

MacCarty (6) names the varieties, simple chronic catarrhal, chronic catarrhal with cholesterosis, chronic catarrhal with papaloma, and writes: "These occur separately or in combination; all three occur with or without stones. Despite the fact that these are the simplest forms or stages of the disease, they are nevertheless the most difficult to diagnose clinically and to treat, either medically or surgically, correctly. They

are those which are followed after surgical treatment by the most frequent unfavorable late sequelae; they are the forms of the disease about which there will always be the question whether they should be treated medically or by cholecystostomy or cholecystectomy."

Clearly, then, medical treatment of this disease requires consideration, and more especially because of the frequency with which cholecystitis is found to be associated with other diseases.

These figures compel us to consider diagnosis and differential diagnosis, which leads to the classification of cases into

1. Those in which medical treatment of cholecystitis is not applicable, because of coexisting disease necessarily requiring surgery.

TABLE II

Comparison of follow-up study on calculus and calculus series. (Kunath, Carl A. (4))

Number of cases reviewed	100	100
Typical Biliary Colic	56%	84%
Pathology of the Gall Bladder, normal	25%	1%
Post-operative course, stormy	17%	7%
Wound infections	8%	1
4 eviscerations		1%
Mortality	8%	2.4%
Cured or improved	69%	84%
Appendectomy	62%	65%
End Results		
Number available for study	85	83
Cured	26%	51%
Improved	43%	32%
Unimproved	22%	13%
Dead	8%	2%
Incisional Hernia reported	4.7%	12%

2. Those in which exist contraindications for surgery, but removable or remediable, and therefore requiring medical treatment.

3. A group requiring surgical treatment combined with medical treatment, that is, all so-called surgical cases.

4. The remaining group concerning which both surgeon and internist agree that medical management alone is indicated.

In some instances diagnosis of gall bladder disease is easy; in others it is difficult, and even when such disease is known to be present, it is often more difficult to determine the presence or absence of coexisting disease elsewhere, and also what part the latter is playing in the production of symptoms and morbidity. Such diagnosis and differential diagnosis will require

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not only the history taken by some one who is familiar with the symptomatology of the diseases in question, but also examination of all of the useful methods and clinical observation of the patient over a period of

TABLE III

Gall bladder disease is associated with	
Appendicitis (7)	50 per cent
Cardiovascular disease (serious) (8)	63 per cent
Angina Pectoris (25 per cent having stones) (9)	25 per cent
Autopsies on diabetic patients over 25 years of age showed gall stones present in (10)	23 per cent
In cholelithiasis, common duct stones present in	18 per cent
In cholecystitis, stones present in	64.5 per cent

time while under controlled management and treatment; i.e., making a therapeutic test.

Having dealt with the problem of diagnosis and differential diagnosis, and disposed of Group No. 1, we now consider Group No. 2, namely, Cholecystic disease requiring surgery but also presenting contraindications which demand medical attention.

These may be dealt with under the heads of Age, Cardiac Disease, Renal Disease, Diabetes Mellitus, and Neuropsychiatric Conditions.

Age (11) in itself is not a contraindication of needed surgery in gall bladder disease, because physiologic age does not necessarily correspond to or parallel chronologic age. Every care should be taken in preoperative study and examination. Operation, anesthetic, and surgeon should be fitted to the patient. The aged, in my opinion, offer less prospect of readjustment on the physiologic level than they do to skillful and artful combination of medical and surgical treatment.

Cardiac Disease is often a contraindication of needed surgical treatment, but that this may be overcome is shown by Walters (11) who operated successfully on a patient 72 years of age, with generalized arteriosclerosis, some dilation of the aorta, and electrocardiographic evidence of recent coronary occlusion; on one, aged 53, with angina pectoris; and one, aged 59, with arteriosclerosis and electrocardiographic evidence of coronary sclerosis; also two cases of bundle branch block.

A. R. Barnes (9) states that approximately 25 per cent of the patients who had angina pectoris have associated cholelithiasis; consequently, the management of cholecystic disease in the presence of coronary sclerosis is a frequent problem, but that cholecystectomy skillfully performed can be tolerated by a patient who has any degree of coronary disease up to and including recent coronary thrombosis. Whenever possible, operation on such a patient should be postponed at least 90 days after acute occlusion, and then should be undertaken by choice only if compensation is satisfactorily established.

The decision whether a patient's symptoms are chiefly anginal or whether they are attributable to the gall bladder, sometimes can be settled only by cholecystectomy.

Surgical treatment of disease of the gall bladder may sometimes be undertaken with a view to improving associated heart disease, and this occasionally

occurs, but that result cannot be relied upon, as a rule.

However, Willis (12) found 39 per cent of a group of patients with chronic cholecystic disease had definite changes in the cardiovascular system, of which hypertensive heart disease and coronary sclerosis were the most common. Seventy-nine per cent of the group were subjected to cholecystectomy; 54 per cent were definitely improved with regard to cardiac symptoms. There was one post-operative death from cardiac disease.

The presence of auriculoventric block is, in general, a sign of a more serious degree of coronary sclerosis and the risk in such cases is distinctly greater, on the average, than it is in cases in which the electrocardiogram shows evidence of bundle branch block only; but this condition—bundle branch block, unattended by other evidence of serious heart disease, must not be allowed to stand in the way of necessary surgical procedure, if the cardiac compensation is satisfactory.

Renal disease is equally serious and more important as a contraindication of surgery of the gall bladder and bile passages, and is probably more frequently the cause of post-operative deaths than is heart disease, because it does not often manifest itself so obviously as heart disease does and, being latent, is therefore overlooked or underestimated as a danger.

Operations on the liver are especially apt to cast an unanticipated burden on the kidneys. The field of operation (gall bladder, bile passages and liver) is normally rich in bacteria and inevitable trauma, existing disease in the tissues, anesthetic, dehydration and fasting readily precipitate a syndrome of maximal gravity.

Interrelation between the liver and kidney has long been assumed and Pytel (13) seems to have demonstrated that certain phylogenetic, anatomic, physiologic and pathologic relationships of the liver and kidney point to an interdependence of the two organs.

He succeeded in demonstrating in his animal experiments that damage to the liver is followed by a definite syndrome, characterized clinically by oliguria, albumi-

TABLE IV

Pathological conditions in the right side which occur alone or in association with gall bladder disease may be erroneously diagnosed as gall bladder disease, and so treated

Urinary:	
	Stone in the right kidney or ureter.
	Nephroptosis—Dietl's Crises.
	Kinked or stricture ureter.
	Hydro-nephrosis.
	Hyper-nephroma.
	Renal tuberculosis.
Other General Conditions:	
	Angina Pectoris.
	Spinal Disease, Arthritis, Metastases and T. B.
	Tabes Dorsalis. Crises.
	Sickle cell anemia. Crises.
	Herpes Zoster.
	Appendicitis.
	Hemolytic Jaundice (stones present in 65% of cases).

nuria, hematuria, nitrogen retention, loss of weight, apathy, and in some cases, death. Pathologically there were areas of necrosis in the liver; in the kidney, stasis of blood in the vessels of the malpighian bodies; hemorrhages into Bowman's capsule, with cloudy swelling and degeneration of the epithelium of the convoluted tubules.

Five to 10 cc. of blood removed from a rabbit with an experimental "hepatorenal syndrome" and injected into a normal rabbit, produced the above described effects.

He assumes the existence of a toxic substance resulting from liver necrosis, circulating in the blood stream and exerting its influence particularly on the kidneys and, to a lesser extent, on other organs.

Clinically this syndrome occurs in diseases of the liver and bile passages, particularly in the post-operative period or following acute traumatic lesions of the liver.

Diabetes Mellitus (14) when not under control is a definite contraindication for major surgical procedure, more especially on the liver and bile passages. Unrecognized symptomless diabetes is especially a menace because operations, anesthetic, deprivation of food, and dehydration are so apt to induce acidosis with its abdominal rigidity, pain, nausea, vomiting and leucocytosis, and these conditions occurring in the onset of coma may not be recognized for what they are, but may be mistaken for some surgical post-operative complication. A blood chemistry is the most important laboratory examination that can be made in preparation for gall bladder surgery.

Diabetes can be easily controlled by well known methods to such an extent that a major operation can be performed with nearly as little risk as in a non-diabetic patient.

The hepatorenal syndrome can best be prevented or controlled by similar methods, possibly combined with transfusion.

In neuropsychiatric conditions the situation is more difficult to determine, but the decision with regard to operation certainly requires an individual judgment for each case.

Having disposed of the important group of cases in which medical treatment will modify or remove known contraindications to needed surgical treatment, there remains the much larger group, including all so-called surgical cases, and these should have the best possible pre-operative preparation and post-operative management.

It may be said that surgeons now recognize and meet this requirement. But it should be emphasized that the best statistics on gall bladder surgery come from those well organized hospitals in which there is skilled and uninhibited collaboration between a surgical staff and a medical staff, accustomed to working together, and in which the members recognize each other's problems, ability and limitations.

There now remains that group of cases in which surgical treatment is not definitely needed, that is, there is no evidence of stones, tumor, or obstruction, but presenting symptoms of functional dyspepsia, not relieved by measures directed to conditions found in the stomach and intestines.

This group usually have mild pain under the right ribs, flatulence and belching, as a rule not definitely associated with the digestive cycle. Roentgenologically they may show either a normally functioning gall

bladder, one poorly visualized, or not visualized. Some of this group will have even typical attacks of gall bladder colic, requiring hypodermic medication for relief. This colic in itself does not necessarily place them in the class for necessary surgical treatment.

That such a group may exist seems to be indicated by the post-operative studies in noncalculous cases (4).

It will be generally agreed that this limited group comprises a small percentage of all cholecystic disease. It is not so obvious that satisfactory results from medical treatment are further limited by conditions inherent in the physiology and biochemistry of the biliary system.

However, it will become clear that success will be greater if aims and methods are made to conform with what would seem reasonably possible in the light of physiologic relations and clinical experience.

What these possibilities and limitations are will be more apparent by a reference to the physiology and chemistry of the biliary system. Recent information derived from experimental surgery, physiology and pharmacology has given us a rational though limited basis for physiological, medical treatment, so that while there is a more definite basis for treatment, there are also equally definite limitations as to what we may hope to accomplish under the existing conditions. Therefore, before hopefully undertaking medical treatment of cholecystic disease as such, to the exclusion of surgery, it will be definitely helpful to review briefly the motor, secretory and chemical mechanisms concerned in this system.

Concerning infection the facts may be briefly summarized: The tissues of the gall bladder, bile passages, liver and adjacent lymph nodes are all the normal habitat of a variety of bacteria, arriving mainly through the blood stream, but also through the lymph channels from the upper respiratory system and the intestines (15). Infection also occurs by reverse peristalsis into the common duct.

The simple presence of these organisms in the tissues does not cause manifest disease. Another factor must be added. Furthermore, their presence in the bile stream does little or no harm and is of relatively little significance.

Many bacteriological studies have shown that the tissues are found to contain bacteria about twice as frequently as the bile (16), nor is their number in the bile at all proportionate to the degree of infection in the tissues.

But it has been demonstrated experimentally and clinically that under adverse conditions such as trauma, stasis, obstruction and perhaps some other conditions which we do not understand precisely, such as shock and impaired blood circulation, the dormant organisms may set up an acute fulminating process which may cause death, become subacute, chronic, or subside entirely.

However, infection is not only an evil in itself, but also acts indirectly to produce a secondary sequence of events.

Inflammation or irritation of the gall bladder is believed to increase the rate of absorption of bile salts by the wall of the gall bladder (17), and thereby reducing the solvent action of the bile, leads to the precipitation of cholesterol and the formation of gall stones, which in turn are apt to cause obstruction and another series of grave events.

Infection, therefore, should certainly be controlled by all means, medical or otherwise; but the medical man should recognize his limitations in this field.

The modes of approach to the prevention or eradication of infection would be prevention and removal of foci of infection in the upper respiratory passages, and hygiene of the bowel. That the latter bears a practical relation to functions of the gall bladder was shown by Lahey and Jordan (18), when it was demonstrated that in 44 per cent of 65 cases of cholecystitis also manifesting signs of colon irritability the gall bladder would fill normally after from five to ten days of bowel management, whereas with the same intravenous dye technique it had previously shown an absence of or inadequate filling. It should be needless to say that such hygiene requires a therapeutic approach based upon the normal and abnormal physiology of the digestive system, and cannot be accomplished simply by the use of laxatives and enemas.

The idea of treating cholecystic disease, including cholelithiasis, by influencing metabolism is very appealing because it suggests the possibility of intervention through the primary phases of pathogenesis.

A glance at what is known concerning the physiology of cholesterol and especially what is unknown, however, is somewhat discouraging.

Unfortunately, cholesterol (the essential part of most gall stones) of the bile does not vary with changes in the total blood cholesterol, nor is its concentration raised by increasing the cholesterol content of the diet (19).

The percentage of cholesterol in the bile of the gall bladder is a result of the absorption of water and salts through the gall bladder wall, which results in a concentration of from five to ten times that of the bile as it enters the gall bladder.

Furthermore, the ability of the bile to hold cholesterol in solution is dependent upon the concentration of bile salts. If the usual ratio of cholesterol: bile salts, which is 1 to 20, up to 1 to 30, for any reason falls as low as 1 to 13, precipitation of cholesterol occurs.

There is no evidence that the body, cholic acid, is derived from cholesterol; feeding the latter causes no increase in the production of bile salts. The precursors of cholic acids in the body are also unknown. The site of its origin is unknown, whether it is formed by hepatic epithelium or is merely brought pre-formed to the liver from other tissues.

That some is formed in the body is indicated by the fact that the bile salts continue to be discharged from a biliary fistula during long periods of starvation; that it is derived from food as well is shown by the increased excretion which follows the ingestion of protein material. So far as is known, the liver is the only situation where the conjugation of taurin or glycochol with cholic acid and the production of the respective bile acids can take place.

In pregnancy, which seems to increase the frequency of gall stones, it is not the hypercholesterolemia (which is not constant), but the normal ratio of cholesterol to cholesterol esters, which is altered. Alteration of this ratio has been considered as an index of liver disease (20 and 21).

If the gall bladder is removed (and presumably, if its function is destroyed by disease) and its acidifying function eliminated from the bile duct system, gall stones of varying composition can be formed at will

by the precipitation of calcium carbonate, which is normally held in solution in bile acid.

There is a further indirect influence exercised by an inflammatory exudate, rich in protein material derived from the blood, which carries an electric charge of opposite sign from that held by cholesterol, pigment, and inorganic constituents. It is believed that as a result of this physico-chemical regulation the deposition of cholesterol, combined in varying degree with other biliary constituents, is effected.

Since it has been shown that bile acids maintain cholesterol in solution and that when they are reduced in concentration, carbonates are precipitated (22), and that acid bile will bring about the dissolution of gall stones (23), it would appear that maintaining or increasing the acidity of the bile would prevent the formation of, or possibly bring about the dissolution of formed gall stones, but the oral administration of sodium dihydrogen phosphate, salicylic acid and glycolic acid, substances known to be eliminated partially by the biliary system, do not influence the pH of the bile (24).

Increasing cholesterol in the diet does not increase cholesterol in the bile. High blood cholesterol does not cause increased cholesterol in the bile. Hypercholesterolemia in itself cannot cause gall stone disease.

The hypercholesterolemia observed in cholecystitis is the result of primary changes in the liver, which is so frequently seen in association with gall stone disease.

The lowering of the cholesterol ester—total cholesterol ratio, which has been observed and assumed to bear a relation to the formation of gall stones, would be difficult to change by any method with which we are at present acquainted. There is some clinical, therapeutic and experimental evidence that the liver is the site of the formation of cholesterol esters and that the diminution of them is an index of hepatic insufficiency.

While the cholesterol esters are usually lowered in acute liver degeneration, in cholecystitis and cholelithiasis, with no obstruction, and no complicating infection of the biliary passages, the blood cholesterol figures are not significantly altered.

From what is known of the complexity of the metabolism of cholesterol, cholesterol esters, bile acids and bile salts, as well as from the great limitation of our knowledge, it appears that there is little prospect of intervening effectively by medical or dietetic measures to a degree that will modify the development or course of cholecystic disease or the formation of gall stones, which so frequently complicates the clinico-pathological picture.

Concerning stasis or complete obstruction, it will be recalled that in other systems, whether respiratory, circulatory, urinary, or gastro-intestinal, extensive severe lesions may be present for a long time with a minimal immediate menace, and relatively mild symptoms; but when stasis or obstruction occurs, the potent character of the symptoms and the malign consequences are directly in proportion to the suddenness of the onset and the degree of completeness with which obstruction is established. A similar series of events and consequences obtains in the biliary system.

Stasis is therefore of the greatest practical importance in the development of cholecystic disease and its complications, because it not only influences the chemical and metabolic functions but, by disturbing the

secretory and motor functions, it contributes markedly to the awakening of a latent, inactive infection to an active process in one of the most vital systems of the organism. This would be very discouraging if it were the whole story, but it is singularly fortunate that, complex though it is, the motor mechanism of the biliary system is the better understood and more amenable to therapeutic attack than are any of the other factors operating in cholecystic disease, and therefore offers the most encouraging field for medical intervention in its disturbed functions.

The complete stagnation of total obstruction does not enter into the discussion in formation of stones because if the obstruction is complete and the gall bladder tied off or functionless, the intraductal roses (300 millimeters of water or more), secretion of bile is suppressed, the ducts become distended with a characteristic fluid (white bile) containing no pigment, bile salts or cholesterol, and bearing practically no resemblance to bile; and no stones can be formed.

If the normal gall bladder is left in communication with the obstructed duct system, the sequence of events is entirely different. Biliary stasis then causes thick greenish bile to collect in the ducts and bladder as a result of the latter's concentrating activities, and the mucinous material which it secretes. After a lapse of weeks the inspissated bile develops an almost tarry consistency.

The functions of the ducts and gall bladder are antagonistic, the former tending to dilute, the latter, to concentrate the biliary fluid. The diluting is at first overbalanced by the concentrating action of the gall bladder, and when this remains in communication with the duct system the net result is a marked inspissation of the bile. There is, however, a tendency with time for the activity of the ducts to overcome that of the gall bladder as it becomes functionless, the biliary constituents disappear, and ultimately the normal contents of the system are entirely replaced by a thin simple secretion of the duct and mucinous material from the gall bladder, producing hydrox.

Stasis, partial or temporary, caused by inhibition of the normal flow of bile, may be produced, (1) by marked changes in the bile, such as thickening, or by partial occlusion of the common duct by a small stone or plug of mucus; or, (2) by change in the normal mechanism by which the gall bladder is evacuated, namely; simultaneous contraction of the gall bladder and relaxation of the sphincter of Oddi. (Spastic biliary dyssynergia (25)).

That such a clinical entity exists has been demonstrated by Best and Hicken (25). They observed roentgenologically and clinically a state of affairs in which there occurred colicky pains, demonstrable spasm of the sphincter of Oddi, with failure of evacuation of the contents of the common duct. Partial or complete relief of the symptoms—pain and colic—with demonstrated evacuation of the common duct, was obtained in several instances by the use of certain nonsurgical measures.

This demonstration provides a rational basis for the prevention and treatment of biliary stasis, and this is the rational approach to the medical treatment of chronic cholecystitis.

Empirical treatment of chronic cholecystitis once consisted in the administration of calomel and salts. Later it reached a degree of elaboration and refinement at the European Spas where a meticulous diet

was given, alkali waters were drunk and salines taken with benefit.

With the advent of biochemistry it was believed that high fat diets were deleterious, in that the sequence of events was cholesterolemia, increased elimination of cholesterol in the bile and precipitation of cholesterol, representing the essential steps in the pathogenesis of gall stones. Present knowledge does not sustain this point of view.

After Meltzer's observation on the evacuation of the gall bladder and the clinical work of Lyon and many others, medical drainage of the gall bladder and biliary system became established as a diagnostic and therapeutic measure, but Lyon has written (26) "Once the definitely chronic stage is reached, the final therapeutic cure is secured only by surgical procedure aided by adequate medical measures directed toward lowering operative mortality and lessening post-operative morbidity."

This statement should be borne in mind despite the favorable reports of this method of treatment.

Feldman and Morrison (27) report of 61 noncalculous, malfunctioning gall bladders, 21 were drained by the Lyon method at regular intervals; 18 were completely relieved of symptoms.

Bile salts have long been used in gall bladder disease. Rosenak and Kohlstaedt (28) treated 63 patients having disease of the gall bladder and liver with bile salts over a period of nine months; in 22 cases of proved lithiasis, pain was not satisfactorily removed by this method of treatment; however, better results were obtained in relief of constipation and digestive symptoms. The treatment was more successful in 16 patients with cholecystitis, without proof of the presence of stones. Pain was relieved in a large proportion of these, and marked improvement in digestive symptoms in all was most striking. In 25 patients with symptoms indicative of gall bladder dysfunction, but in whom positive evidence of actual disease may be lacking, very satisfactory results were obtained. When bile salts were discontinued temporarily in these patients, all symptoms returned. Similar results could not be obtained by means of dietary control alone or by means of cathartics.

Brown and Dolkart (29) used Keto-cholanic acids. They selected for study a group of 131 patients who had been observed and treated for upper abdominal distress for a varying length of time. Sixty-five of these showing Roentgenographic evidence of dysfunction with and without stones were accepted for a test of therapy.

Seven variations in the therapy were used, namely:

- (1) Hourly feedings of milk and cream as in ulcer, and antispasmodic.
- (2) Hourly feedings and Keto-cholanic acids.
- (3) Hourly feedings, Keto-cholanic acids and antispasmodic.
- (4) Bland diet and Keto-cholanic acids.
- (5) Bland diet, Keto-cholanic acids and antispasmodic.
- (6) Low fat, low cholesterol diet only.
- (7) Low fat, low cholesterol diet, Keto-cholanic acids and antispasmodics.

All patients were ambulant. The mixture of Keto-cholanic acids contained the oxidation products of all the natural bile acids found in human bile in the normal proportions. Administration was orally in the form of 3¼ grain tablets, one tablet three times a

day. In four patients in whom no improvement in visualization was observed following 60 days of this medication, the dose was doubled.

Two criteria for evaluation of the results of therapy were used: (1) Frequent cholecystographic evidence of improvement; (2) Subjective changes.

The most consistent subjective improvement occurred in those patients receiving the Keto-cholanic acids. In the majority of instances the subjective improvement was found to parallel the objective improvement as revealed by repeated cholecystographic examinations. The exceptions were found in those patients in whom large stones had been demonstrated. These manifested marked subjective improvement but little change could be observed Roentgenographically.

Following the dietary and Keto-cholanic acid therapy, some previously nonvisualized gall bladders were visualized, and filling defects due to stones were noted, which were not previously seen.

In a few cases in which stones were reported in the Graham-Cole test, they were not seen on succeeding visualizations. Three of the patients with nonvisualizing gall bladders had normally visualizing gall bladders after therapy.

In those patients who gave histories of frequent, repeated attacks of gall bladder colic, these attacks would decrease in frequency and severity and gradually disappear after approximately two weeks of therapy.

In three instances untoward results were obtained in hourly feedings of milk and cream and Keto-cholanic acids simultaneously. One patient had distress in the epigastrium and distention; these symptoms subsided after changing to a bland diet. In two patients typical attacks of colic occurred; one of these on hourly feedings of milk and cream and Keto-cholanic acids, had colic, a slight diarrhea and passed some granular material which was examined and found to be typical faceted cholesterol gall stones, 2 to 4 millimeters in diameter.

The authors' interpretation of these results is guarded, especially concerning Roentgenologic evidence of improvement, as this may be due to (1) actual increased activity of the gall bladder, due to improvement in the pathologic gall bladder wall; or (2) improved mechanical flow resulting from increased amount of bile from the liver.

The need for care in interpreting Roentgenological improvement is indicated by the observation of Lahey and Jordan (18) who found 40 per cent of 65 cases of cholecystitis also manifesting signs of colon irritability; the gall bladder would fill normally after 5 to 10 days of bowel management, whereas with the

same intravenous dye technique it had previously shown an absence or inadequate filling.

Clinically, the patients of Brown and Dolkart obtained relief, not obtainable by other methods of treatment.

Gradual introduction of the treatment is desirable if the patient has been on a much restricted diet. The authors consider failure to improve clinically as manifested by continued pain, jaundice, repeated colic after the foregoing management, a definite indication for surgical intervention. Although they included in their series all forms of pathologic changes, termed chronic cholecystitis, no case was referred for surgery.

From what has been stated in the discussion of stasis and the use of Keto-cholanic acids it would appear that a combination of choleretics and cholagogues with a bland diet and antispasmodics would afford means for the rational medical treatment of a selected group of chronic cholecystic disease. However, this group will be limited and it is well to bear in mind the limitations of the therapeutic methods available.

One can do no better than to quote from A. A. J. Kelly in "Osler's Modern Medicine" of thirty years ago. "The physician, however, in many cases, may lead his patient into a condition of virtual cure, that is, latency or sterility of the biliary tract; but he must recognize his limitations and by a judicious balancing of his abilities and limitations not subject his patient too long to a useless medical treatment when early surgical intervention may restore him to health, whereas delayed, it may not only add to the miseries of a miserable existence, but actually hasten final termination."

Under the title of "Medical Treatment of Cholecystic Disease," this paper has dealt with physiology, pathology, diagnosis and treatment intentionally, because facts now available indicate emphatically that we do the patient and the art of medicine an injury when we think of, and practice the treatment of "cholecystic disease." Treatment should comprehend "the patient with cholecystic disease." Surgical treatment should be constantly in the mind of the internist and medical management should be a part of all surgical cases. Medical treatment, at best, is limited to certain possibilities, and likewise, although the surgeon can remove stones and a diseased gall bladder, the operation does not remove conditions which caused the disease or the secondary effects of the disease which existed.

In conclusion, I should say, the field for medical treatment of cholecystic disease, as such, is small and stony, and although not entirely sterile, any growth that occurs is apt to be malignant.

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Editorials

PERNICIOUS ANEMIA AND ACHLORHYDRIA

ONE often reads that achlorhydria can be found occasionally in cases of definite pernicious anemia. Alsted (1934) collected thirty-two such cases from the literature. It has been thought also that achlorhydria is usually present for years before pernicious anemia develops, but cases have been reported in which this was not the case.

To help settle these questions, Rozendaal and Washburn (*Ann. Int. Med.*, 11:1834-1837, 1938) received the records of 906 consecutive cases from the files of The Mayo Clinic in which a definite diagnosis of pernicious anemia was made, and found achlorhydria in all of them. This finding agrees with that of Sturgis (*Ann. Int. Med.*, 10:283-289, 1936) who studied 600 cases. In none of The Mayo Clinic cases was there a return of free hydrochloric acid following treatment for the anemia. Hurst (*Guy's Hosp. Rep.*, 80:244-247, 1930), however, has reported four cases in which the secretion returned following treatment for the gastritis.

In thirty-six of the cases at The Mayo Clinic a study of the gastric secretion had been made from two to twenty-one years prior to the onset of pernicious anemia. In almost every one of these cases the blood was studied at the first visit, and in only two cases was there a slight anemia. This was of the microcytic hypochromic type. In only two of the thirty-four cases was there any free acid in the stomach years before the pernicious anemia appeared. In these two cases the previous examination was made nineteen and seventeen years respectively prior to the onset of the anemia.

These two series of cases of Rozendaal and Washburn and Sturgis indicate, then, that the presence of free acid in the stomach of patients with apparent pernicious anemia should make a physician very distrustful of his diagnosis in regard to the nature of the anemia. It seems clear also that in all but a few cases the achlorhydria is due not to the anemia but to a condition probably hereditary and perhaps congenital, which long antedates the appearance of the anemia.

W. C. Alvarez, Rochester.

IRON IS NOT EXCRETED BY THE INTESTINAL MUCOSA

IT has been stated by many observers that several of the metals, and particularly salts of iron, are excreted by the mucosa of the colon. At the last meeting

of the American Society for Clinical Investigation, Stephen Maddock and Clark Heath (*Jour. Clin. Invest.*, 17:533, 1938) of Boston, reported some interesting and apparently decisive experiments in which they first grafted various parts of the digestive tract with their blood supply into the abdominal wall of the dog. Iron was then given, either by mouth or parenterally. Before and after giving the drug, bits of tissue from the exposed mucous membrane were snipped off, stained for iron, and studied histologically.

No definite increase in iron was found in the bits of tissue from the bowel of the animals given iron. At necropsy large amounts of iron were found in the liver and spleen, and smaller amounts in the kidney and skin, but none was found in the mucosa of the stomach, duodenum, ileum, cecum, or colon.

According to the investigators these findings agree with those of some other workers in the field of iron metabolism, all indicating that there is no appreciable excretion of iron by the intestinal mucosa.

W. C. Alvarez, Rochester.

THE SPIROCHETES OF THE GASTRIC MUCOSA

IT has long been known that spirochetes are to be found in the gastric glands of a large percentage of laboratory animals. They have been found in the dog, cat and rabbit. Curiously, they are commonly seen in the canaliculi which run up into the substance of the parietal, or acid-secreting cells of the stomach. Doenges (*Proc. Soc. Exper. Biol. and Med.*, 38:536-548, 1938) now reports the finding of spirochetes in the gastric glands and parietal cells of 100 per cent of some forty-three *Macacus rhesus* monkeys studied. Such spirochetes were not found in the glands of the intestinal mucosa.

Doenges studied also sections from 242 well preserved human stomachs removed at necropsy, and found spirochetes in 43 per cent. Usually only a few were found after considerable search, and large numbers were found in only eleven of the specimens.

It is possible, of course, that in some of these cases the spirochetes entered into the tissue during the agonal period or even after death. Someone now should look for them in material removed at operations on the stomach.

W. C. Alvarez, Rochester.

Book Reviews

Digestive Tract Pain: Diagnostic and Treatment. By Chester M. Jones, M.D. The Macmillan Company, New York, N. Y., 1938.

This small volume of 143 pages deals with pain and other similar sensations as referred to the alimentary tract, deals with it as a clinical symptom, as of diagnostic importance and discusses the physiological substrate underlying its creation in the body. But essentially the author utilizes an old but well recognized experimental method for his interpretation of the symptoms, namely such subjective and objective data as are obtained by distending each segment and part of the alimentary tract with an inflated balloon. A small balloon was swallowed to different levels of esophagus, stomach and small intestine, and it was inserted through colostomies, ileostomies and into the rectum. Clinical subjective tracings are tabulated, Pain, heartburn, fullness, distress, heat and cold recorded, and subjective sensations of distress are studied in their relationship to the body surfaces and to the various abdominal and thoracic segments.

The location of the origin of disturbance (the distended balloon) and the surface area of the pain are correlated and interpreted for each organ and for each segment of the alimentary tract. No profound attempt is made to cover all of the experimental, clinical and philosophical concepts and publications referring to the study of pain in the past. To do this would have occupied a volume in itself. Though due respect is given to the concepts of Head, Lennander, Mackenzie and others, the author prefers to rely on the clinical diagnosis as established in each case, and to study each particular individual by his own kymographic approach, utilizing his own physiological interpretation.

The most interesting part of the book is that which deals with the subjective symptoms of pain and heartburn at the various esophageal levels. While much of the work is a repetition of that of Hurst, and of the more recent study of Babby, the analyses of the subjective thoracic sensations and surface areas are very enlightening, particularly from a clinical viewpoint. Again, the references of pain originating in the various levels of the small intestine are timely and are accurately located. The new interest

in the various forms of granulomatous lesions of the small intestine, particularly the ileum, and the various forms of segmental colitis makes this chapter the more valuable. Unfortunately too many pain zones of the ileum, jejunum and colon coincide in general location. As in the case of Head zones, the areas demarcated by Jones often overlap and duplicate each other, so that clear-cut clinical conclusions as to the origin of a pain cannot be attained.

The book should be read and re-

read, and the careful conclusions in each individual case closely scrutinized. The author is a careful, honest clinician of established reputation. His case histories will bear close analysis and seem well established as to diagnosis. His conclusions, are, like the author himself, reserved, never overstated, and always scrupulously modest and honest. The volume can be heartily recommended for careful study by advanced students and clinicians who spend

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their hours in the consulting room at the baffling problems of trying to correlate abdominal pain with the organ and the lesion from whence it originated.

B. B. Crohn.

Maribuana. By Robert P. Walton. J. B. Lippincott Company, Philadelphia, 223 pages, 1938.

As many physicians know, hashish or cannabis indica, long used in the East as an intoxicating drug, has invaded the United States and is becoming a big problem, particularly in the Southwest, where peddlers have been distributing cigarettes known as reefers, muggles, or goof butts, to

school children, negroes, prostitutes, and others.

The smoking of these drugged cigarettes by boys and girls appears to be widespread. It has become a new fad, and something must be done to stamp out a growing industry. Habituation leads, much as it does with opium, to the destruction of character and the ruination of nerves. The drug affects the whole nervous system. There are hallucinations, sometimes inordinate and senseless laughter, and a feeling that the subject is floating away. Sometimes the dreams are horrible nightmares, and sometimes the smoker develops an exaggerated irritability which leads

to violent rages. Cases are known in which the habitue ran amuck and committed murder.

Walton has made a most extensive study of the problem from every point of view, and his very interesting volume should be of great help to those who are struggling to stamp out the trade in this narcotic. The most distressing feature of the problem is that peddlers are reaching out to enslave the children in our schools.

Physicians will find the book very readable. The chapter containing the descriptions of the visions experienced by a number of able writers will be found particularly interesting.

Our Common Ailment. Constipation: Its cause and cure. By Harold Aaron. New York, Dodge Publishing Company, 192 pages, 1938.

Perhaps the commonest of those dysfunctions of the body that come with civilization is constipation. Because of it millions of men and women today are dosing themselves regularly with laxatives, purgatives, and indigestible oils and gums. Some who have the digestion of an ostrich get along fairly well; others who have a more sensitive intestine are in trouble all the time. We of the medical profession are not always very helpful. Too often we run to fads: the physician who has some favorite laxative prescribes it for every patient, and those physicians who now prescribe a rough diet or some mixture of gum and oil commonly threaten with dire disaster any patient who dares to use an enema or a mild laxative. Few physicians today seem to know or to face two facts: One, that the treatment for constipation must be fitted to the individual, and the other, that what works for a patient one week may not work at all the next week.

Under these circumstances, people need more help, and many need a book which will explain many things, answer many questions, and combat much false information and belief. Here at last is a book by a sane, well-informed writer who has supplied the three things so much desired. He tells of the causes of constipation and of the difference between the mythical high and low enemas. He shows up the buncombe in modern campaigns for alkalization of the body or for fastening on baby a lifetime purgative habit (she will cry for it); and it routs the boogies of autointoxication, spastic colitis, and ptosis.

Although written primarily for a lay audience, it is well worth reading by medical men and even by consulting gastro-enterologists. Many could profit from the lessons it teaches, and many would be much interested to learn facts about the composition of the various gummy substances and laxatives. Every young physician

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The Diets of Olympic Athletes of the Past and Present (Die Ernährung der olympischen Kämpfer in Vergangenheit und Gegenwart). By Adolf Bickel. A booklet of 35 pages and 2 illustrations. Deutsche Verlagsgesellschaft M. B. H., Berlin, 1938.

The Relation of the Quality of the

Dietary Protein to the Course of the General Metabolism (Ueber die Beziehungen der Qualität des Nahrungseiwisses zum Ablauf des Betriebsstoffwechsels). By Adolf Bickel. Paper, 100 pages. Benno Schwabe & Co., Verlag, Basel, 1938.

The former of these two works is an address delivered by Bickel at the University of Athens; the second is a monograph published under the auspices of the Schweizerische Medizinische Wochenschrift. They contain some material of immediate interest to the student of nutrition; in addition, they suggest hypotheses that should inspire a great deal of further research. In view of the ideas con-

cerned, a somewhat detailed presentation seems desirable here, especially since the author's style frequently becomes so involved that few readers, whatever their linguistic accomplishments, will find it easy to go through all of the material in the original language.

Schenk's study of the diets of athletes who participated in the Olympic Games in Berlin in 1936 showed that lean meat was the central article of diet; it was commonly eaten rare, sometimes even raw. Bickel's thesis is that the instinctive preference of athletes for certain proteins results largely from a factor hitherto unrecognized in dietetics—a striking difference among the proteins in the way they affect metabolism. This factor is distinct from others now generally known, such as the completeness of the protein in essential amino acids. Though it so far eludes identification, it betrays itself in at least three ways: (1) the ratio of oxidizable material to total nitrogen in the urine, (2) the ratio of carbon to nitrogen in the urine, (3) the amount of glycogen stored in the liver. These are the three determinations upon which Bickel's work is based.

The two urinary ratios depend upon three chemical procedures. The first is the customary Kjeldahl procedure for nitrogen. The second is the determination of oxidizable material; the procedure consists in treating the sample with an excess of potassium iodate in sulphuric acid. This oxidizes a variety of urinary constituents; the amount of oxidation is measured by the amount of left-over iodate. This yields a figure called the Vakatsauerstoff, hereinafter abbreviated "V-O." The third procedure consists in determining the total carbon by oxidizing it in the wet way with a mixture of bichromate-sulphuric acid and silver bichromate, and absorbing the carbon dioxide. The figures for total nitrogen, total carbon, and Vakatsauerstoff yield two urinary quotients, C:N and V-O:N. The chemical significance of these ratios remains to be settled; the remarkable thing about them is the way they change when the type of protein is changed in a diet otherwise kept constant.

Bickel found that these ratios remained reasonably constant both in animals and in man if the diet was uniform. But if the diet alternated between normal and protein-free sharp differences resulted. In a given diet, if the casein was replaced with a casein modified by irradiation with gamma-rays from mesothorium, the C:N fell while the V-O:N, after some irregularities, went up strikingly. Various experiments were done on the substitution of amino acids for whole proteins; thus tyrosine was found to raise the V-O:N markedly

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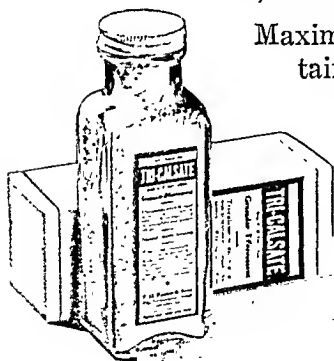
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PEPTIC ULCER—THE EFFECT OF HIGH PROTEIN DIET ON THE BEHAVIOR OF THE DISEASE	- Charles Windwer, M.D. and Milton J. Matzner, M.D.
THE VALUE OF GASTROSCOPY IN THE DIAGNOSIS OF PHYTOBEZOAR: CASE REPORT	- Julian M. Ruffin, M.D. and Robert J. Reeves, M.D.
ULCERATIVE COLITIS OF 28 YEARS' DURATION WITH RECOVERY	- William Z. Fradkin, M.D.
TREATMENT OF OPERABLE RECTAL CANCER IN POOR SURGICAL RISKS	- George E. Binkley, M.B., Tor.
A PRACTICAL METHOD OF ANALYZING THE PRECIPITATING FACTORS PRODUCING PEPTIC ULCER	- Edward J. Callahan, M.D. and Donald W. Ingham, M.D.

An Open Letter to the Physicians of North America

Do you realize that 60 per cent of all symptoms in general practice arise from the digestive tract?

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Is diagnosis of digestive diseases easy?

Apparently not. The old rule of thumb—"appendix, ulcer, or gall bladder" is no longer useful. We are becoming gradually acquainted with the disorders and diseases of the colon and reducing this information to some semblance of order. Physiology, bacteriology, chemistry, parasitology, clinical observation, animal experimentation, roentgenology, nutrition, allergy and psychology are the organized methods of approach to a fuller knowledge of

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Place the contents of 4 envelopes of Knox Gelatine in an ordinary drinking glass. Add 4 ounces of cold milk and allow to soak for five minutes. Add 2 more ounces of milk and stir until thoroughly soaked. Then place glass in small cooking kettle of hot water until gelatine milk mixture is thoroughly dissolved. Add 2 more ounces of cold milk, which will bring the temperature to a satisfactory warm drink of about body heat. A tablespoonful of prune juice or a few drops of any bland flavor like vanilla may be added.

Total: 8 ounce liquid — about 250 calories

"The Knox Fruit Stir"

Place the contents of 2 envelopes of Knox Gelatine in an ordinary saucer or cereal dish. Add 8 tablespoonfuls of any desired fresh or canned fruit juice, such as grape juice. Let soak for five minutes and eat with teaspoon.

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while lowering the C:N. In other experiments, various amino acids were administered not only by mouth but also subcutaneously.

In particular, a very extensive experiment was done in which diets containing casein, as a standard, were compared with other diets in which everything was the same except the protein. In those cases in which casein was compared with complex protein-containing foods like potatoes, the control casein diet was mixed with potato starch, etc., in such proportions as to make it reasonably certain that the total nitrogen, carbohydrate, fiber, and calories in the two diets were equal. The only

difference between control and test diet, then, was in the type of protein. The results showed that it was possible to arrange the various proteins on a linear scale according to their effects on the urinary quotients and liver glycogen. At one end of the scale came gelatine, wheat gluten, and edestin, with low urinary quotients and low liver glycogens; at the opposite extreme were the proteins of soy beans, green beans, carrots, potatoes and oats.

Evidently this makes possible a new dietary classification of proteins, a classification not identical with others based on high or low glucose equivalent, specific dynamic action,

amino acid content, and plant or animal origin. It also suggests new possibilities for the control of the general direction of body metabolism by prescribing the type of protein to be eaten. It should also challenge investigation of the exact chemical nature of the metabolic processes reflected in the new urinary quotients.

Frederic T. Jung, Chicago.

Abstracts

CONNOTATIONS

H. J. SIMS, M.D.

Denver, Colorado

Albucasis, an Arabian physician residing in Spain, during the eleventh century recorded the first case of extra-uterine pregnancy.

Gibson made the first report of a diseased gall bladder in a male child 12 years of age, in 1722. The diagnosis was made at autopsy.

The yellow color of rhubarb was once thought to contain the active ingredients capable of exciting the flow of bile.

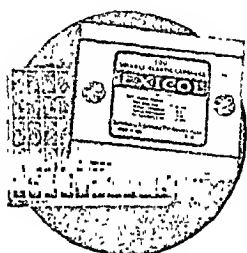
The humoral theory of disease was formulated by Philolaos of Croton. He based his work on that of Anaxagoras. Hippocrates agreed with Anaxagoras and believed any disturbance of the equilibrium of these humors resulted in disease.

The idea of mothers chewing for infants dates back to antiquity. Whether the idea developed as a supplementary feeding or whether it replaced milk is not known. The writer has seen mothers chew potatoes and other articles of soft food and then force the bolus within an infant's mouth. According to Vallembert, Galen prescribed bread soaked in broth or soups for nurslings. The same author refers to a mixture of flour or bread cooked in water known as pap and then mixed with milk as panada. He dated the beginning of the use of pap in the year 1465. The mixture was first chewed by the mother or nurse and given to the infant. This method of feeding continued for over a century. Ettmuller in 1698 and Astruc in 1746 questioned the advisability of such feedings and yet as late as 1830 special pewter spoons were manufactured for the purpose of controlled feedings.

It is not known in general that President Cleveland suffered from a sarcoma of the upper jaw. In the year 1893, he secretly entered a private yacht and underwent an operation for resection of a portion of the upper jaw. An artificial vulcanized rubber jaw was made to fit into the defect. This artefact was so well adapted that no apparent defect in speech was noticed.

Anatomical dissections by Hippo-

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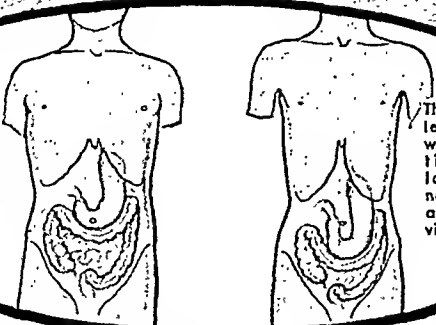
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*Amer. J. Digestive Diseases, Vol. 5, No. 6, p. 348, August, 1933.

**J. Lab. and Clin. Med., 19:567, 1934.

Relations of
stomach and
colon in normal
body type as
contrasted with
asthenic type
(at right)



This type is of-
ten associated
with constipa-
tion. (Note
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crates were likely limited to the Barbary Ape and to domestic animals although occasionally he must have observed abdominal organs of man at the time of embalming. Dissections of the human body through religious teachings were not permitted. A dead body was thought contemptible and yet it was too sacred to be subjected to whimsical curiosity from which nothing could be gained. His concepts of the aqueduct of Sylvius, the hypophysis, cerebral nerves, sympathetic ganglia, and the third and fourth ventricles of the brain were gained from dissection of the brain of oxen. He stated that the uterus contained

two compartments. The right testicle and the right chamber of the uterus were capable of producing a male child. It is evident that he had not observed a human uterus.

Galen continued to teach the humoral theory of Hippocrates. As long as the humors existed in proper relation to each other, health was maintained. If they became diminished or thickened, or were retained in some remote area in the body, disease was manifested. In the summer months, yellow bile predominated; during the winter months, phlegm was abundant. In health, the blood was consistent with joy and laughter; but if it in-

creased, man became moody. Yellow bile also denoted health, but when it grew excessive, man became worried. Too much black bile rendered an individual sad and morose, and too much phlegm induced distaste for food.

Stephen Hales, an English clergyman, invented the first instrument for recording blood pressure in 1733. An interval of one hundred and sixty-three years elapsed before a practical and accurate instrument was devised by Riva-Rocci. In 1856, Faivre successfully recorded in man the actual blood pressure. He connected a mercury manometer with the femoral artery and observed the blood pressure to be 120 mm. of mercury. The first practical instrument for blood pressure undertakings was devised by von Basch in 1880. The British Medical Journal in 1880 criticised physicians who depended upon blood pressure instruments for any gainful information. Such information bankrupted a physician's diagnostic acumen.

Long before Jenner successfully introduced his method of smallpox vaccination, the Chinese recognized that fleas of a cow suffering with vaccinia might be used to immunize an individual.

During the Ming Dynasty (1368-1644 A. D.), a materia medica was compiled under the orders of the Emperor by a number of medical men. It recognized a plant known as Mahuang from which our present alkaloid ephedrine is extracted. The pomegranate is also mentioned as a drug. Because of its many seeds, it was symbolic of many offsprings. This fruit was and is now a favorite nuptial offering.

Shen Nung, who ruled China in 2737 B. C., is recognized as the originator of the Chinese materia medica.

During the time of Confucius and for many centuries afterwards, the human body was believed to consist of metal, water, wood, fire and earth. As long as these five elements existed in proper relations, health existed. Any disturbance in these elements was manifested by disease. The five major organs, the heart, liver, lung, spleen, and kidneys, were associated with the five planets, five colors, five tastes, the five climates, and the five elements.

Lazzaro Spallanzani, an unusual anatomist, physicist, and geologist, was born in 1729 and died in 1799. He became a priest at the age of 26 and was appointed professor at the College of Emilia. He soon became interested in spontaneous regeneration, animal reproduction, and artificial fecundation. He made in 1788 his greatest contribution to physiology. He recognized the behavior of the muscular coat of the stomach and of its mucous membrane in the process of digestion. He swallowed the food enclosed in perforated ivory tubes and upon its

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removal noted that the food had undergone chemical change. He thus inferred that the muscular coat of the stomach was concerned only in mechanical digestion. He fed sponges tied with threads to different birds and upon their withdrawal, he was convinced that chemical digestion had actually taken place. These experiments were not accepted; no less an authority than John Hunter opposed such conclusions.

The mechanism of parenchymatous respiration was partially described by DaVinci in 1591. He ironically remarked, "All animals perish in an atmosphere in the absence of a burning flame." Spallanzani in 1791

demonstrated gaseous interchange and combustion as a natural phenomenon in all animals. Several Italian physiologists believe Spallanzani discovered the white blood cells in 1768.

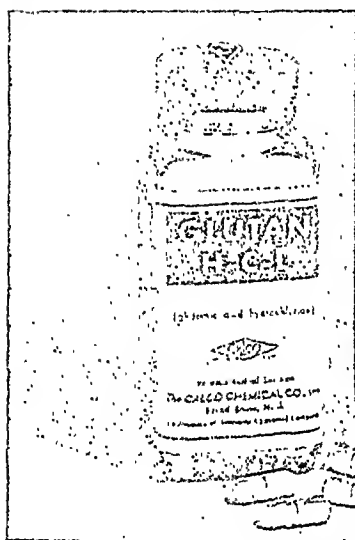
Orfila, a pioneer toxicologist, was born in 1787. He was the author of various text books on toxicology. In the year 1817, his first text appeared on medical chemistry; within another year, a second book was presented on the treatment of poisons and asphyxia.

As late as 1775, any applicant seeking an honorary medical degree from St. Andrews University could do so upon the recommendation of two phy-

sicians and the payment of ten guineas.

Ignaz Philip Semmelweiss, born in July, 1818, was graduated in 1844 from the University of Vienna. Puerperal fever at this time was thought to be a form of typhus fever because of its endemic character. The milk theory and suppression of the lochia were also taught as a cause. Semmelweiss became interested in its endemic tendencies, and through an accident, discovered the etiological factor. He had occasion to autopsy a man having died from a generalized septicemia following an infection of a finger. He noted in his post-mortem findings the analogy of septicemia and puerperal fever. Hospital attendants invariably performed autopsies, prepared ligatures in the morgue, and without formality attended women in labor. Semmelweiss concluded that the disease might be carried from the dead to the living. He immediately ordered all attendants to wash their hands in chlorinated lime before attending obstetrical cases. The mortality rate declined. Considerable controversy arose as to the cadaveric theory. At the time he was compiling statistics in support of his conclusion, an outbreak of puerperal fever occurred in his obstetrical ward. He believed a woman admitted to the ward suffering from a discharging wound in the hip to be the endemic source. To his cadaver theory, he then added that living organisms were a most probable source of the fever. This was protested by Pesth, Braun, Hebra the famous dermatologist, Rokitansky a pathologist, Klein, a renowned obstetrician. Both Semmelweiss and his theory were so unpopular that he severed his affiliation as an instructor at the University of Vienna. In 1860, his text appeared on puerperal fever. He performed in Hungary the first ovariotomy in 1863. During this year, he suffered attacks of melancholia, and two years later he was admitted to the insane asylum.

Jean Paul Marat, born in 1743, received an honorary degree at the age of 32 to practice medicine. The requirements for graduation were endorsement by two physicians and the payment of ten guineas (about fifty dollars). Previous to receiving his medical degree, he practised veterinary medicine. At the time or soon afterwards, he published a paper on diseases of the eye and another on gleet. In his community, he enjoyed considerable reputation because of the rapid recovery of a well-known woman who was a patient of his. The drugs he used were carefully guarded. At a later date his secret remedy was found to consist of chalk and water. Apprehensive of a possible revolution, he began the publication of a weekly paper in 1789. His writings were chiefly ironical satires directed toward



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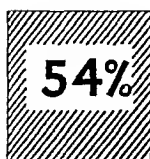
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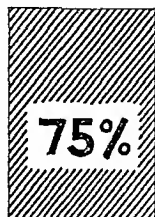
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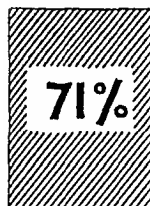
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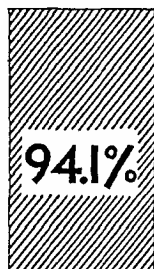
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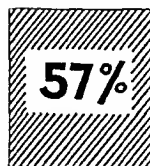
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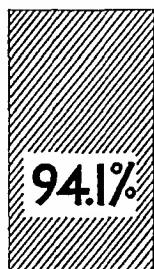
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*Ann. Int. Med. Vol. 9, No. 8, Feb. 1936

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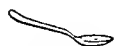
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the King and subordinates. He fled to England. Two years later he returned to Paris and lived in seclusion. The following year the King was beheaded, and he then became master of the situation. A young woman opposed to his authority gained entrance to his palace on a false pretense, thrust a knife through his chest, and killed him instantly.

EUSTERMAN, GEORGE B.

Common Gastro-Intestinal Emergencies and Their Medical Aspects. Annals of Internal Med., 12:306-316, Sept., 1938.

A wide variety of diseases and disorders frequently gives rise to disturbances predominantly of gastro-intestinal nature and of sufficient severity to constitute an emergency. Differentiation of an acute abdominal condition that requires prompt surgical interference and a nonsurgical one is the most important function of the physician.

In chronic lesions of the digestive organs the more common complications, perforation, hemorrhage, and obstruction, frequently give rise to conditions which constitute an emergency. Serious disorders engendered by disease remote to the abdominal organs, those of pulmonary, vascular andcretory systems in particular, are chiefly of a gastro-intestinal nature and frequently overshadow the less spectacular but more diagnostic symptoms which are indicative of the organ that is at fault.

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Hanes M. Fowler, Fort Wayne.

WAKEFIELD, E. C. AND MAYO, CHARLES W.

Functional Sociologic Disorders of the Colon. J. A. M. A., Vol. III, No. 18, Oct. 29, 1938.

This article, with the intriguing and provocative title that it bears, is couched in ideas which are indicative of the new trend in clinical medicine. The recrudescence of an interest by the physician in the social background of functional disease is actually a return to the approach which, in the past, the general practitioner was wont to follow. His knowledge of the

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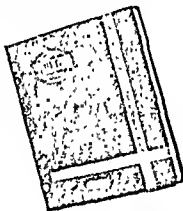


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intellectual, moral, religious and genetic background of each of his patients stood him in good stead in diagnosis and treatment.

Drs. Wakefield and Mayo approach the problem of functional disorders of the colon with this same attitude. The use of placebos is positively eliminated from their armamentarium. An appeal to the intellect of the patient is felt to get much better results. They conceive of the problem as arising from a social crisis and being activated by one or more of several factors. These are listed as heredity, congenital faults, environment, irregular habits, food allergy, laxatives, systemic disease, or fear of disease. They make no bones about the matter that although the diagnosis may be arrived at easily, the solution of the problem is far more difficult; for the cause often lies in the defects in our educational system, form of government, religious attitude, morality concepts, and often heredity. The etiologic factors are well discussed, and the presenting symptoms and signs are outlined. The bowel habits can vary from diarrhea to constipation. Typical of the diarrhea is the secretion of large amounts of white stringy mucus. The history is most important in bringing out the vital factor involved. The diagnosis is made by elimination based upon stool studies, sigmoidoscopy, X-ray, gastric analysis for free HCl, and a basal metabolic rate.

The treatment should not include medication, except for the diarrhea, which can be helped to a greater extent by informing the patient as to the etiology of his symptoms. The constipation should be treated with flake or crude agar in cereal or milk.

The cure of functional disorders, they feel, rests upon the adjustment of the individual to his social conflicts. Perhaps it would be much better if the social order could be adjusted to the individual.

Henry H. Lerner.

MIXTER, CHARLES.

The Value of Palliative Surgical Therapy in Advance Carcinoma of the Gastro-Intestinal Tract. *New Eng. Jour. of Med.*, Nov. 10, 1938.

Actuated by an extensive experience and profound sympathetic interest in patients with advanced carcinoma, Dr. Mixter emphasizes the conviction that every possible means to relieve suffering, even at the expense of a high-operative morality, ought to be attempted in such individuals.

The intractable pain of the early, ulcerated lesion or the late metastases are almost unbearable. The development of fistulae following necrosis of the tumor, and the consequent peritonitis or abscesses, he feels should

not be allowed to occur. The vomiting or tenesmus due to mechanical obstruction can all be avoided by radical extensive surgical procedures if necessary.

Multiple resections in several stages should be carried out even though the lesion may be seemingly removable. Metastases, he feels, are not always a contra-indication to resection of the primary growth. Often the results from both the comfort of the patient and the duration of life following such procedures are surprisingly gratifying. The modern colostomy does not in any way incapacitate an individual. The life of lingering wretchedness which is contrasted to one relatively free of suffering in the operated individual is by itself an irrefutable argument for early radical surgical procedure in hitherto so-called advanced inoperable carcinoma.

Henry H. Lerner.

NOBLE, R. L. AND ROBERTSON, J. D.

The Effect of Hypertonic Solutions on Gastric Secretion and Intra-ocular Pressure. *J. Physiol.*, Vol. 4, p. 430, 1938.

Cats under nembutal anaesthesia were used. Gastric secretion was induced by histamine. In so far as gastric secretion is concerned, 30% NaCl (5 cc. per kilo) and 50% glucose (17 cc. per kilo) both caused a dilution of haemoglobin which rapidly returned to normal and inhibited both the acidity and volume of juice secreted. 5% NaCl (5 cc. per kilo) and 50% glucose (5 cc. per kilo), solutions of equal osmotic pressure, caused a similar transitory dilution of haemoglobin but had little or no effect on gastric secretion.

M. H. F. Friedman, Detroit.

SCHIFF, L.

Gastric Secretion in Man. Observations on the Repeated Injections of Histamine and on Transient Achlorhydria. *Arch. Int. Med.*, Vol. 61, p. 774, 1938.

In a trained human subject, repeated (799) subcutaneous injections of histamine over a period of 4½ years were given without harm. There was no overfatigue of the HCl-secreting mechanism. Spontaneous temporary disappearance of free HCl and pepsin occurred.

M. H. F. Friedman, Detroit.

MUSSER, J. H. AND SODEMAN, W. A.

Gastro-Intestinal Expressions of Avitaminosis. *Southern Med. J.*, Vol. 31, p. 397, 1938.

Avitaminoses may give rise to gastro-intestinal symptoms; on the other hand, gastro-intestinal disturbances may result in deficiency expressions. The significance of Vitamins A, B-complex, and C is reviewed.

M. H. F. Friedman, Detroit.



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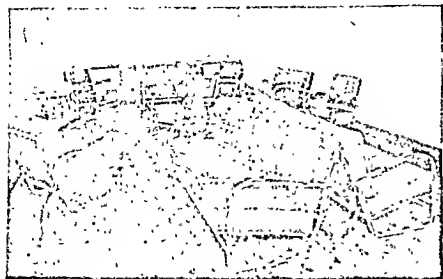
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PROPOSED REORGANIZATION OF BIOLOGICAL ABSTRACTS

The Board of Trustees of BIOLOGICAL ABSTRACTS, in order to insure the continued solvency of this publication and to extend its usefulness to an increasing circle of scientific workers, has evolved a plan which deserves support from individuals and societies. Briefly, it is proposed to issue the ABSTRACTS in the form of five separate parts, each of which will cover a group of cognate sciences.

I. **GENERAL BIOLOGY**, to include General Biology, Biography-History, Bibliography, Evolution, Cytology, Genetics, Biometry and Ecology. Price \$4.00.

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It is hoped that this partition of the subject matter now covered by the complete edition of the ABSTRACTS, will attract many subscribers to whom the cost of the present publication—\$25.00—would be prohibitive. All subscribers will receive the complete index of the combined volume. Abstracts will appear within two to three months of the time of publication. The editorial policies and standards will be guided by Committees appointed by the representative societies in each field.

Under this new plan, BIOLOGICAL ABSTRACTS may confidently look forward to carrying out the indispensable function of making available to all workers, with promptness and accuracy, the current scientific output in those special and related fields.

Alwin M. Pappenheimer.

1939 MEETING MISSISSIPPI VALLEY MEDICAL SOCIETY AT BURLINGTON, IOWA

The fifth annual meeting of the Mississippi Valley Medical Society will be held in the new \$500,000.00 Municipal Auditorium (to be ready June 1, 1939) at Burlington, Iowa, September 27, 28, 29, 1939. The magnificent new Auditorium at Burlington, only two blocks from the headquarters hotel, will afford the Society the largest and finest meeting place it has ever had. A wonderful Exhibit Hall is being planned which will afford both technical and scientific exhibitors, the largest floor space in the history of the Society.

The Society's officers for 1939 (elected Nov. 20, 1938) are as follows:

President—M. Pinson Neal, M.D., Columbia, Mo. (Elected 1937).

President-Elect—John T. Hanna, M.D., Burlington, Iowa.

1st Vice-President—Joel W. Hardesty, M.D., Hannibal, Mo.

2nd Vice-President—Lindon Sead, M.D., Chicago, Ill.

3rd Vice-President—William M. Hogle, M.D., Keokuk, Iowa.

Secretary-Treasurer—Harold Swanberg, M.D., Quincy, Ill. (Re-Elected).

The following were recently elected to membership on the Board of Directors of the Society:

A. H. Bitter, M.D., Quincy, Ill.; James Graham, M.D., Springfield, Ill.; C. F. Harmon, M.D., Springfield, Ill.; W. L. Hanson, M.D., E. St. Louis, Ill.; C. C. Maher, M.D.,

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FOURTH ANNUAL POST-GRADUATE INSTITUTE

The Philadelphia County Medical Society desires to announce formally, the completion of its scientific program for the Fourth Annual Postgraduate Institute to be held in the Bellevue-Stratford Hotel, Philadelphia, during the week beginning March 13, 1939. The subjects to be considered are those embraced by the terms BLOOD DYSCRASIAS and METABOLIC DISORDERS. These will be further subdivided for convenience in instruction into eighty-six clinical lectures, with open forum discussion for each topic, delivered by as many individual specialists of national distinction.

The pre-eminent position of Philadelphia as a medical center in the past has been justified by its large array of first class hospitals and con-

tributory institutions, and that conservative scholastic atmosphere so essential to careful and dependable research. Despite the development of medical centers in other areas, Philadelphia has continued to maintain its enviable position and it has been the desire of the Philadelphia County Medical Society to release to its own members and to those of the medical profession in general, the results of the labors so diligently conducted within the walls of the city's several medical schools.

The tremendous advances in the medical sciences since the World War have increased the demands of the lay public for medical information. The development of the channels for communication have familiarized the public with medical conditions and terms to such an extent that the physician must keep himself at least informed if not intensely educated concerning the most recent work in the medical field. He cannot conduct his practice along the older lines without continuing his education in the new.

The Postgraduate Institute aims to fill this need and the participants may be assured that they will unquestionably profit by the program to be presented.

THE COMMITTEE.

LEVIN, M.

Morbid Hunger in Relation to Narcolepsy and Epilepsy. J. Nervous Mental Dis., Vol. 88, p. 414, 1938.

Cases of periodic somnolence accompanied by morbid hunger. Periods of days or weeks in which patient eats excessively and shows motor unrest and mental symptoms. Levin suggests that untimely and prolonged inhibition of higher centres results in this hunger and motor unrest. These centres may be those shown by Fulton to exist in frontal lobes, excision of which produced increased appetite and gastro-intestinal hypermotility.

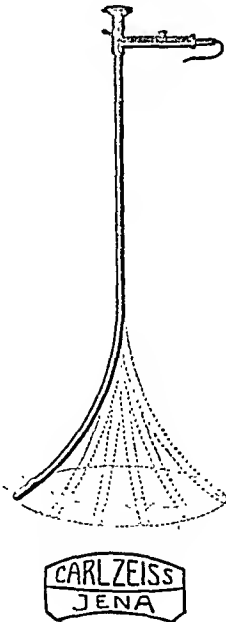
M. H. F. Friedman, Detroit.

MAASSEN, R.

Sekundäre Pellagra nach Gastro-Enterostomie (B₁ — Komplex — Avitaminose). Deutsche Med. Wochenschr., Sept. 23, 1938.

In patient with a gastro-enterostomy there developed a condition typical of pellagra insofar as skin changes and psychic disturbances showed. A diet rich in vitamin B₁ and B₂ was without effect. However, after 6 daily injections of nicotinamide, the skin changes, gastro-intestinal disturbances, and pellagra psychosis disappeared.

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Studies on Humans with a New Secretagogue Meal

By

ROY UPHAM, M.D., F.A.C.S.*

and

FRANK SPINDLER, A.B., M.D.†

NEW YORK, NEW YORK

WITH the determined conviction that studies of gastric secretions under proper controls would evolve data which would be of value in diagnosis, we have combed the literature thoroughly, and the meal, as evolved by Wilhelmj, appears to be a far step in the approach to the ideal test meal. The results so far reported by Wilhelmj have been confined to studies on dogs and we present this discussion as an attempt at evaluation on human beings.

The more commonly used test meals (shredded wheat biscuits, arrow root cookies, bread or toast, with water or weak tea) are very low in their secretagogue effect thus rendering them inadequate tests of the acid secreting power of the stomach.

"Histamine is a powerful stimulant of the hydrochloric acid secretion yet its action is abnormal in that it stimulates solely the secretion of hydrochloric acid and not that of pepsin and other organic constituents." The alcohol test meal acts as an irritant and its action as a secretagogue is therefore abnormal. Our results with this meal have not been uniformly consistent.

Wilhelmj stated the particular qualifications of the meal as evolved by him are (a) a high secretagogue effect and action through normal channels. (b) Relatively low in organic material and buffer substances thus making for a more accurate titration. (c) No marked change in consistency while in the stomach. (d) Ability to use phenol red as an indicator in order to determine the true composition of the secretions entering the stomach. (e) Liquid consistency so that phenol red is not absorbed by solid particles. (f) The test meal should have no acid neutralizing or combining power and finally (g) it must be possible to standardize the test meal before use. The meal was made up in a two per cent solution as follows:

1. 40 grams of Liebig's extract (Lemco Brand) are dissolved in one liter of distilled water.
2. Add 30 mgm. of the sodium salt of phenol red dissolved in 33 cc. of 1/10 N NaOH.
3. Add 20 cc. of a 20% solution of sodium carbonate. The solution is now alkaline.
4. Add slowly with constant stirring one liter of 1/10 N hydrochloric acid. The solution is now acid to litmus paper.
5. Allow to stand until a heavy flocculent precipitate settles out.
6. Filter until crystal clear.

This gave us two liters which was ample for use in six tests. The meal should have a titration value of between 11-22 cc. of 1/10 N acid. If it runs higher than these figures more alkali may be added to bring it within these limits.

In the course of experimentation we found that better colorimetric readings were obtained by using

twice the amount of phenol red and sodium hydroxide suggested in the preparation of the test meal.

"By preparing such a solution all undesirable material was removed by the acid added, and secondly, sufficient base was supplied to care for the non volatile acids. Thirdly, by leaving the solution slightly acid with hydrochloric acid, its acid neutralizing and combining powers would be saturated." To adapt the test for clinical use in the physicians office, it was found practical and time saving to prepare several liters of the meal at one time. The preparation of a single meal requires at least two hours time, but multiple quantities can be elaborated in the same period. The preparation of the meal requires a person adequately trained in chemical procedures. It may be stated that the extraction is no more time consuming than that of an ordinary fractional meal. Subsequent chemical procedures and the added mathematical computations involved are so time consuming that it appears the meal, in its present form, is not applicable as ordinary office procedure, but must be classed more as a research implement.

Reviewing some of the complexities and difficulties arising in experimentation we found, that in order to handle a large group of cases, it was necessary to have available a properly equipped laboratory both as to space required and equipment needed.

The taste, appearance and ease of administration through tube trained patients and the use of the meal by mouth is so acceptable that all elements of psychic depression of the gastric physiology were reduced to a minimum. Varying our technique somewhat from that suggested by Wilhelmj, our meals (in a designated number of cases) were prepared with acid values which ranged from 9 cc. of 1/10 normal hydrochloric acid per 100 cc. to 30 cc. of 1/10 normal acid.

The amount of meal administered varied from 150 cc. to 500 cc. In each case, however, specimens were removed every half hour until the stomach emptied. The meal was administered to a large series of gastrointestinal cases previously studied and an attempt was made to secure controls by its use on normal human beings. The latter group consisted of medical students who volunteered their services. In the entire series of cases a fractional study (arrow root crackers and water or the alcohol-phenolsulphonphthalein test meal) was available for comparison. The number of patients we could reasonably handle at one time did not exceed twelve in number with two trained technicians in charge, and the mathematical computations required the remaining time of a working day.

Experimentation with the quantity of test meal fed to patients revealed the fact that smaller amounts, in contrast to the work done on dogs, gave the greater number of half hourly yields. There were a few ex-

*Associate Professor of Medicine at New York Medical College Head of the Section of Gastro-Enterology and Attending Gastro-Enterologist at Flower Fifth Avenue Hospital and Metropolitan Hospital.
†Clinical Assistant in Medicine-Gastro-Enterology, Flower Fifth Avenue Hospital and Metropolitan Hospital.
Submitted April 21, 1933.

ceptions to this. At first 500 cc. of the meal was used as a standard for both male and female patients. Our results in so far as the number of half hourly specimens obtained were low; especially in the group with gastric pathology. As would be expected with post-pyloric lesions, and angulation of the duodenum due to visceroptosis, a greater number of yields was obtained regardless of the amount of meal administered. In the remaining cases, the meal being liquid, was found to empty fairly rapidly. After a series of tests 300 cc. portions were found to give the greatest number of return specimens taken every half hour. Patients with a previously diagnosed achylia gastrica, emptied the stomach rapidly regardless of whether 300, 500, or 600 cc. was administered to them. In most of the terminal gastric catarrh cases the use of 300 cc. gave us at least three specimens. In comparing our work with that done by Mr. James Wills at the Medical College of Virginia several years ago on a meat extract preparation, it was interesting to note the similarity of results in many respects. He states, "that the response to meat juice is somewhat more rapid than that to the Ewald test meal. Also the fall is somewhat sharper. It is worth note in this latter consideration that with meat juice the emptying time of the stomach is about an hour and three-quarters, while with the Ewald test meal the emptying time is two and a half hours."

Attempts were then made to determine any changes in acidity when the patients took the meal by mouth or tube. Each patient had at least three extractions performed at different times. The manner in which this was done was to introduce the meal via the tube the first two investigations, and lastly the patient was allowed to drink the meal and the tube was passed in fifteen minutes. The changes in titration of acidity in the yields were not marked. In fact, the type of curve of each investigation was so similar as to render the differences negligible in our estimation.

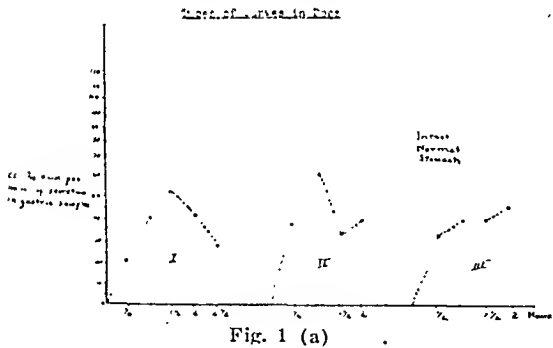


Fig. 1 (a)

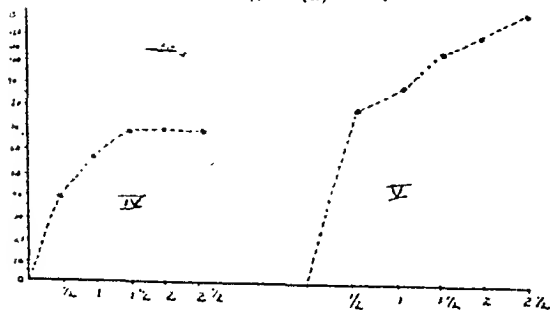


Fig. 1 (b)

Only one untoward reaction was evidenced by a woman who stated that she became extremely nauseous and vomited after returning home. This patient, it was noticed, ran a great amount of bile in each specimen from the first yield on. The fact that she had a posterior gastro-enterostomy performed some time previous to the experiments throws some light on that situation.

There are five types of normal curves described by Wilhelms in his work on the intact normal stomach of dogs and the whole stomach isolated from the intestine.

Type I comprises about half the total number, types II and III about 30%. Curves of type IV and V are due to lessened duodenal regurgitation and absorption of non acid fluid from the gastric contents.

The majority of so called normal cases in our series follow a curve as illustrated:

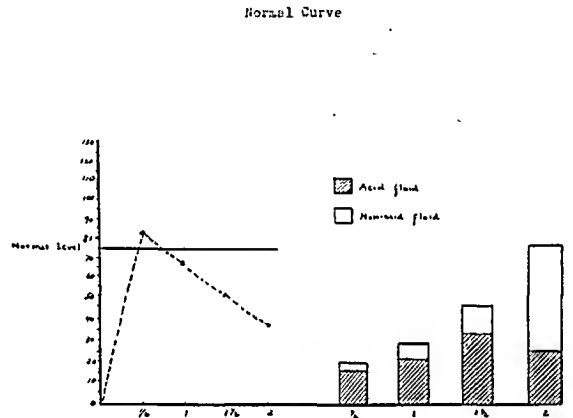


Fig. 2

Here we notice a sharp rise in the acid secretion during the early part of the experiment and a fairly sharp fall in the acid curve, during the latter part. This is in concurrence with the findings of Wills as quoted previously in this paper. The result is obvious when we consider that of all the test meals evolved, the meat extract or so called secretagogue meal acts to a greater extent as a physiological stimulus than any of the other procedures. Therefore, we have accepted the above charted curve as the predominant normal curve, and based our succeeding findings on it. The exceptions to this were found in the following:

Group I—Duodenal ulcer with pyloric obstruction.

Here we see a very sharp rise in acid in the first

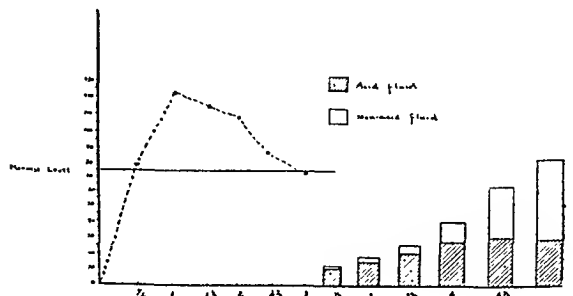


Fig. 3

hour with a very gradual tapering off in the acid curve and a greater number of specimens. In fact only limitation of time prevented further withdrawal of half hour specimens beyond the third hour. The acid fluid in the early yields composed the greater part of the total fluid in the stomach, but as we drew toward the second and third hour yields, there was a greater addition of non acid secretion to the gastric contents. Apparently there was some reabsorption of water by the stomach wall but this is not marked. Duodenal regurgitation also played a part as a neutralizing factor in the latter part of the experiment.

Group II—Duodenal ulcer without obstruction.

In this group there is again a very sharp rise in the

Duodenal Ulcer Without Obstruction

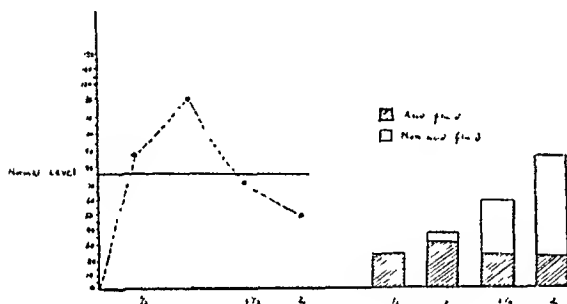


Fig. 4

acid curve in the first hour and almost as sharp a drop in the second hour. The acid fluid remained fairly high throughout the yields. As a rule we were unable to obtain more than four specimens in similar cases. The secretions pouring into the stomach cavity however, remained fairly high in acid composition.

Group III—Sub-Acid Gastric Catarrh (slight acid production).

The curve is low and plateau type. The amount of

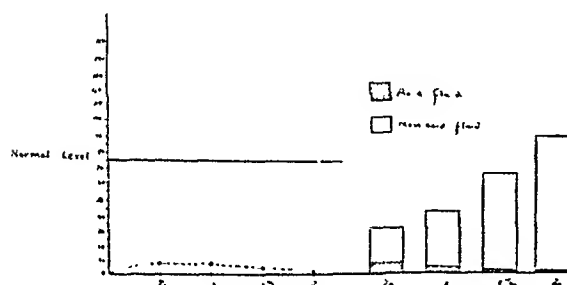


Fig. 5

non acid fluid is greatly out of proportion to the acid fluid. The secretions poured forth by the stomach wall are in the main non acid. As a general rule its acid content is so low that frequently it dilutes the acid content of the test meal. In many of these cases the alcohol and the Ewald meal called forth no acid production at all, again illustrating the more apparent stimulatory effect of the secretagogue meal.

Group IV—Total acidity. In this group there was no acid production. In fact the acid in the test meal was neutralized by the gastric and extra-gastric secretions in all specimens.

Cholecystitis and cholelithiasis cases gave us no curve of diagnostic value at present. It may be stated that as a general rule gall bladder disease produced lower acid curve than normally found. Possibly in a larger series of cases there may be more definite conclusions arrived at.

Let us briefly compare some of the results obtained with the alcohol-phenolsulphonphthalein, cracker and water and the secretagogue meals. It was found that the alcohol test often developed no acid whereas the secretagogue and arrow root cracker meals did in the same patient. The stomach definitely reacted to the beef extract preparations, which was found to be more stimulating to acid production than carbohydrates. In some cases the secretagogue meal produced some acid even where histamine had failed. This was particularly observed in cases of terminal gastric catarrh where no acid was produced in any specimen by the use of histamine. In such cases the use of the secretagogue meal frequently called forth acid production in the second hour even though there may have been an anacidity in the first hour yields.

A further observation was made in comparing the secretagogue meal with the arrow root cracker meal. Here it was seen that the former called forth an early secretion of acid by the stomach which dropped consistently from the second hour specimen. On the other hand a direct reversal of this curve was seen with the cracker meal. Here the curves recorded a later elevation of acid. It would seem therefore that the secretagogue meal has the power of stimulating the stomach to immediate activity, and as there is no substance in the meal to bind the hydrochloric acid produced, exact figures for gastric acidity can be computed. The secretagogue meal is ideal in that it gives a true picture of the acid curve produced by the stomach, whereas, with the ordinary Ewald cracker meal, there is a binding of the hydrochloric acid by the meal in the first hour which confuses and makes unreliable the acid values. The secretagogue meal gives exact knowledge of the time of production and volume of acid produced in the stomach and a definite rate that it is neutralized by a non acid secretion. We are able to determine the relation of the acid to the non acid secretion and we are further able to evaluate the amount of non acid secretion produced by the stomach in comparison with the amount of regurgitated material from the duodenum. In subsequent papers we hope to evaluate the curves of true gastric ulcer, and to reveal the position of the so called neuroses in relation to gastric pathology.

The Bete Noir of gastric diagnosis has been the large group of cases which have been classed as functional neuroses.

The authors feel that the fact can be established that with the earliest trauma of the nervous system and psychic instability there is a variance in the nerve balance of the stomach, and with that there are quantitative and qualitative changes in the acid and the non acid secretion of the stomach which up to this time have defied evaluation.

It would appear that the secretagogue meal would detect these changes in gastric secretion and a large group of cases which, while they may have their origin in nervous imbalance, will be shown to have disturbance of gastric function which can be based upon abnormal physiology.

In future experimentation attempts will be made to

alter the meal considerably by increasing the per cent of the solution prepared. We have already increased the amount of phenol red over the quantity suggested by Wilhelmj with clearer and more consistent results.

METHODS OF ANALYSIS

The analysis consists of two procedures: (1) titration of a sample of the test meal and of the samples removed from the stomach. (2) determination of the per cent of phenol red in the samples removed from the stomach.

The procedures as outlined by Wilhelmj are briefly:

1. Titration of the test meal and of the gastric samples.

5 cc. of a centrifuged sample of gastric contents or an uncentrifuged sample of the original meal is diluted with 75 cc. of distilled water and placed on a water bath for 30 minutes. Six drops of brom cresol purple are added and the titration is performed using 1/20 N NaOH. The result is expressed as cc. 1/10 N acid per 100 cc. of gastric sample or test meal. The end point is a rich wine colored purple. The titration value obtained is for total acid.

2. Determination of the per cent of phenol red in the gastric samples

5 cc. samples of the original test meal and of each of the gastric samples are placed in 15 cc. centrifuge tubes. Add 2 cc. of 20% sodium tungstate. Then add 2 cc. of 1.33 normal sulphuric acid and mix by inverting the tubes. Stopper the tubes. Allow to stand 1 to 1½ hours until a precipitate settles out. Centrifuge at high speed for 10 minutes. Decant the supernatant fluid into graduated centrifuge tubes. Reduce the volume to 8 cc. Add 1 cc. of 20% NaOH mix and centrifuge again. Compare the gastric samples with the sample of the original test meal in a colorimeter and determine the per cent of phenol red present. Set the standard at 5 mm. and make the comparison on this basis.

Bile tinged gastric samples may be matched by adding a small amount of picric acid to the standard.

For very diluted gastric samples, equal parts of the original test meal may be added and correction in calculation made as follows: The per cent of phenol red in the diluted sample minus 50 times 2 equals the per cent of phenol red in the original undiluted sample.

Bile, in the gastric sample may be tested by a Pottenger ring test.

In the calculations we must determine: (a) The acid in the test meal corrected for dilution. (b) The extra acid. (c) The acid concentration of the gastric secretions. (d) The per cent of phenol red. (e) The total fluid. (f) The acid fluid. (g) The non acid fluid. (h) The per cent of acid fluid.

We determine (a) by multiplying the cc. of tenth normal acid in the original test meal by the per cent of phenol red in the gastric sample. The result is subtracted from the acidity of the gastric sample to give us (b). The acid concentration of the gastric secretions (c) is derived by dividing the extra acid by the decrease in the per cent of phenol red (100% phenol red) and multiplying by 100. The total fluid (e) is shown by the decrease in the per cent of phenol red (100% phenol red). The acid fluid (f) is derived by dividing the extra acid by 1.7 (Hollander, F. "Studies in gastric secretion; Composition of gastric juice as a function of its acidity"). The non acid fluid represents the difference between the total fluid and the acid fluid. It consists of mucus and mucoid secretions of the pyloric and fundic areas, fluid of secreted acid which was neutralized and regurgitated duodenal secretions.

EXAMPLE

Test meal—20 cc. 1/10 normal acid per 100 cc. Gastric samples:

30 minutes	— 40
60 minutes	— 50
90 minutes	— 50
120 minutes	— 52

Per cent of phenol red:

30 minutes	— 85%
60 minutes	— 65%
90 minutes	— 50%
120 minutes	— 25%

1. To determine the acid in the test meal corrected for dilution—multiply the cc. of 1/10 normal acid in the test meal by the per cent of phenol red.

20 x 40 equals	8 cc.
20 x 50 equals	10 cc.
20 x 50 equals	10 cc.
20 x 52 equals	10 cc.

2. To determine the extra acid—subtract the acid in the test meal corrected for dilution from the acid in each gastric sample.

40 — 8 equals	32
50 — 10 equals	40
50 — 10 equals	40
52 — 10 equals	42

3. To determine the acid concentration of the gastric secretion—divide the difference in the per cent of phenol red (100% PSP) into the extra acid and multiply by 100.

32 ÷ (100-85) x 100 equals	214
40 ÷ (100-65) x 100 equals	114
40 ÷ (100-50) x 100 equals	60
42 ÷ (100-25) x 100 equals	56

4. To determine the total fluid—subtract the per cent of phenol red from 100.

100 — 85 equals	15
100 — 65 equals	35
100 — 50 equals	50
100 — 25 equals	75

5. To determine the acid fluid—divide the extra acid by the constant 1.7 and multiply by 100.

32 ÷ 1.7 x 100 equals	10
40 ÷ 1.7 x 100 equals	24
40 ÷ 1.7 x 100 equals	24
42 ÷ 1.7 x 100 equals	25

The non acid fluid is the difference of the acid fluid subtracted from the total fluid.

SUMMARY AND CONCLUSIONS

1. The meat extract meal is a more exact and constant meal than any previously reported.

2. The test does not lend itself readily for use by the average practitioner. It is more the character of a laboratory procedure, and adequate facilities are necessary for its use, together with the assistance of trained technicians.

3. It gives a great deal more information than any other procedure as to the actual amount of HCl produced by the stomach and the time it is evolved as well as the amount of non acid and acid fluid added to the gastric contents by the stomach wall and duodenal regurgitations.

4. The secretagogue meal gives absolute figures as to the amount of hydrochloric acid produced by the stomach and eliminates the error produced by other meals which have ability to combine with the hydrochloric acid and produce false values.

5. A larger series of cases will be attempted before further definite conclusions are arrived at.

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Peptic Ulcer of the Esophagus

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THIS study was made in an effort to clarify the diagnosis of peptic ulcer of the esophagus, to offer certain diagnostic criteria which must be fulfilled before the diagnosis can be established, and to point out an etiologic factor which previously has been overlooked. The literature is chaotic—many cases have been reported without adequate verification; some authors have based their diagnosis only on the presence of an ulceration of the esophageal mucosa without inflammatory signs; others on the presence of a high free acidity and periodic epigastric pain or substernal distress.

The disease is characterized by dysphagia, subxiphoid distress occurring one to two hours after meals and relieved by food or soda, hemorrhage and occasionally, perforation. It differs from peptic ulcer elsewhere in that certain definite conditions which are known must be present before it can occur. Aurelius (1), Hurst (8), Friedenwald (5) and Stewart (17) have all pointed out that the two conditions necessary for the production of peptic ulcer of the esophagus are the presence of heterotopic gastric mucosa in the esophagus, or a patent cardia through which gastric juice is constantly regurgitated into the esophagus. Both of these conditions may exist together, but one or the other must be present. None of these authors suggests any abnormality which might cause this patency of the cardia. This we propose to do later in this discussion. Stewart and Hartfall (17) found a marked association with diseases in which vomiting is a prominent feature, and in association with gastric and duodenal ulcer. However, they suggest that aberrant gastric mucosa must be present. Friedenwald and his coworkers (5), in 1928, were able to produce experimental chronic ulcers in the esophagus of dogs by traumatizing the esophageal mucosa and then bathing the traumatic ulcer with 10 per cent hydrochloric acid. They found that the esophageal mucosa rapidly healed if the hydrochloric acid was withheld.

The first case report of this condition was by Albert in 1839. The histologic pathology was first reported by Quinke in 1879. In 1926, Von Hacker and Lothiesieu collected ninety-one cases, but very few were verified by autopsy. In 1929, Friedenwald and his coworkers (6) gave an excellent summary of the literature and reported thirteen cases from their own practice, all verified by roentgenologic examination and esophagoscopy. In the available literature of the past ten years, excluding Friedenwald's thirteen cases, there are thirty, all verified either by biopsy through the esophagoscope or at autopsy. There are several other cases which are called peptic ulcer, but are either acute, associated with diabetes or tuberculosis or are in some other way of doubtful origin and cannot be considered as true peptic ulcer of the esophagus.

Chevalier Jackson (10) reported eighty-eight cases in 1929, twenty-one active and sixty-seven healed, found in 4,000 consecutive cases in which esophagoscopy was performed for disease of the esophagus, and could find no evidence of increased patency at the cardia, but he made no report of the roentgenologic findings.

Hunt and Stewart collected eleven cases in 1934, and reported three of their own. Stewart and Hartfall (17) found one case in 10,000 consecutive autopsies and gave as the incidence, 0.6 per cent of all autopsies, in a review of the literature. E. Sköld (16) stated that the occurrence is 0.03 to 0.16 per cent of all lesions of the esophagus.

Because of the confusion existing in the literature over the diagnosis of peptic ulcer of the esophagus, we offer the following diagnostic criteria:

1. The ulcer must be unassociated with systemic disease. This condition is made because of the tendency to call any ulceration of the esophagus a "peptic" ulcer, even in the presence of diabetes and tuberculosis. We do not imply that systemic disease renders one immune to peptic ulcer, but that in the presence of certain diseases an ulcerated mucous membrane

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is more likely to be a result of the disease than a separate entity.

2. The ulcer must be seen at esophagoscopy or at autopsy.

3. Free gastric hydrochloric acid must be present.

4. The ulcer must be chronic.

5. The symptoms must be relieved by peptic ulcer therapy and dilatation.

In the discussion of etiology, many authors (Hurst, Stewart, Friedenwald, Aurelius) mentioned the presence of aberrant gastric mucosa in the lower third of the esophagus, where all these lesions occur, and the regurgitation of gastric hydrochloric acid through a patent cardia. None, however, suggested why the cardia is patent. In only one case, that of a child of three with a congenital, short esophagus, was the length of the esophagus or the presence or absence of diaphragmatic hernia mentioned in the literature of the past ten years. There have been seven patients with peptic ulcer of the esophagus in The Lahey Clinic in the past ten years, verified by esophagoscopy and satisfying the requirements mentioned above. Of these, six had either short esophagus, diaphragmatic hernia or both. The other patient had aberrant gastric mucosa in the lower third of the esophagus. We believe this to be of great significance. It is obvious that wherever there is gastric mucosa there is always the potentiality of peptic ulcer, and it was shown by Friedenwald that a constant bath of hydrochloric acid will produce an ulcer in the absence of aberrant gastric mucosa. The two essential factors, then, for the production of peptic ulcer of the esophagus need not be present simultaneously, but one or the other must be, and it is our belief that short esophagus and diaphragmatic hernia have been overlooked in the cases reported heretofore, and are a definite factor in the production of peptic ulcer of the esophagus.

Roesler (15) suggested that cardiospasm, as such,

TABLE I
Age and sex incidence (from the literature)

Years	Male	Female
0-10		1
11-20		
21-30	2	
31-40	3	1
41-50	6	2
51-60	4	3
61-70	1	
71-80	2	
Totals	17	7

may play a part in the etiology of peptic ulcer of the esophagus, but it is more likely that cardiospasm is an effect rather than a cause, and is brought about through the inflammatory reaction around the ulcer. We have reviewed sixty cases of cardiospasm, uncomplicated by other gastro-intestinal conditions, in all of which esophagoscopy was performed. These patients were seen in the clinic during the past five years. In none of them has a peptic ulcer been detected subsequent to treatment.

A striking characteristic of the disease is its most

frequent occurrence during the fourth and fifth decades. The age and sex incidence of the cases reported in the literature are given in the table. In six case reports, the age and sex were not given.

In Friedenwald's series of thirteen (included in the table) the sex incidence was more evenly divided, six males and seven females. In our short series of seven, there were three males and four females; one, fifty-six years; two, sixty years; two, sixty-six years and two, seventy-five years of age.

In our series, roentgenologic examination revealed diaphragmatic hernia and short esophagus together in four cases; diaphragmatic hernia alone in one and short esophagus alone in one. In the seventh case neither of these abnormalities was found but subsequent autopsy revealed heterotopic gastric mucosa. Five of our seven patients gave a history of typical ulcer pain associated in the later stages with dysphagia and regurgitation of undigested food. One patient gave a history of dysphagia only. The other

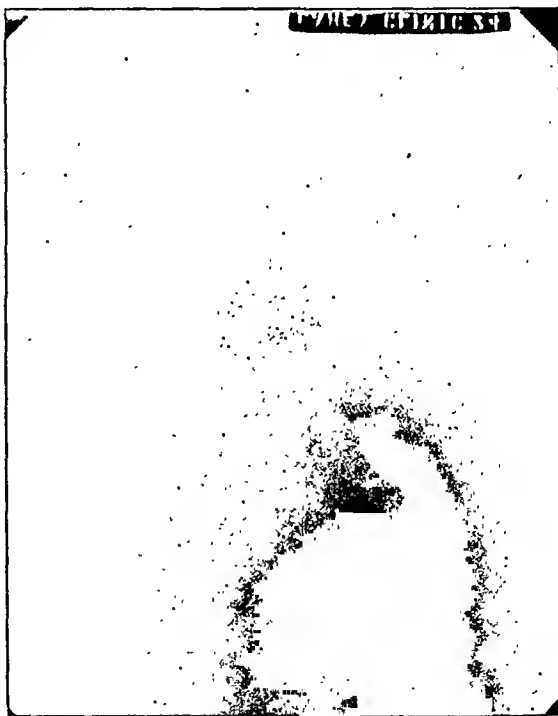


Fig. 2 — Case 1

patient had only the symptoms of cardiospasm; in this case, the first gastric analysis showed no free acid. This is a frequent finding in cardiospasm, and was probably due to inability to pass the tube into the stomach. Later, free acid was found in this case also.

All seven patients did well on Sippy management without local treatment except dilatation except one who required phrenicectomy before relief was obtained. Esophagoscopy a month later revealed healing and the patient remained free from symptoms. There are many cases in the literature in which local applications of 10 per cent silver nitrate solution directly to the ulcer were of great benefit in ameliorating pain and hastening healing, though most authors reported



Fig. 3—Case 2

the use of alkali therapy in conjunction with the local treatment.

Many small, asymptomatic diaphragmatic hernias are seen in the course of a gastro-enterological practice, and occasionally a patient with pain, vomiting or hemorrhage in whom only a diaphragmatic hernia is demonstrable by the roentgenogram. Usually these patients do well on ulcer management and the diagnosis is left at diaphragmatic hernia. Wilkinson (18) (1934) reported a study of seventy patients with diaphragmatic hernia, of whom forty had symptoms suggestive of peptic ulcer, yet of these, esophageal ulcer was found in three cases and gastric or duodenal ulcer in seven. There is no mention made of esophagoscopy in these forty patients. It is our belief that if esophagoscopy were done in these patients, peptic ulcer would be found in more of them, and further that peptic ulcer of the esophagus is not as rare a condition as the reports in the literature lead one to believe. Wilkinson also found the majority of his patients had a short esophagus and stated that "it seems probable that most of these are of congenital origin, but it is unlikely that the defect has always been present. If this were true, more hernias should be discovered in younger individuals, whereas the average age is fifty-four." It is unlikely that a short esophagus is a complication of peptic ulcer of the esophagus caused by the inflammatory reaction and scar tissue formation, since in the majority of cases it is present with diaphragmatic hernia as a predisposing factor.

Our seven cases are reported briefly below.

CASE REPORTS

Case 1. A woman, aged sixty, was admitted to the clinic on February 7, 1932. For three months previous to her

admission, she had had dysphagia on attempting to swallow solid food and, for three weeks previous to admission, some subxiphoid pain about an hour after meals, relieved by taking soda or food. Liquids caused no symptoms.

Physical examination revealed evidence of cerebral sclerosis; otherwise her examination was negative. On laboratory examination a hypochromic anemia was found. Gastric analysis showed 36 per cent free hydrochloric acid. On roentgenologic examination after a barium meal, a short esophagus was revealed, with a diaphragmatic hernia involving about a sixth of the stomach (Fig. 1). In the esophagus just above the hernia an ulcer niche was seen. Esophagoscopy revealed scar tissue, about an inch in length, involving the entire lower surface of the esophagus, in the center of which, on the posterior wall, was an ulcerated area about 0.5 by 1.5 cm. The patient was placed on ulcer management with immediate relief of pain, and was given an occasional dilatation. On roentgenologic examination a year later no ulcer niche was seen, although the short esophagus and diaphragmatic hernia were still present. Her blood count was normal. At this time the patient was working.

Case 2. A woman, aged sixty-six, entered the clinic on July 7, 1933, because of hematemesis and dysphagia. Five years previous to admission she was seized with a severe pain in the interscapular region, which lasted three to four weeks and was followed by another hemorrhage. For six months previous to her admission she had suffered

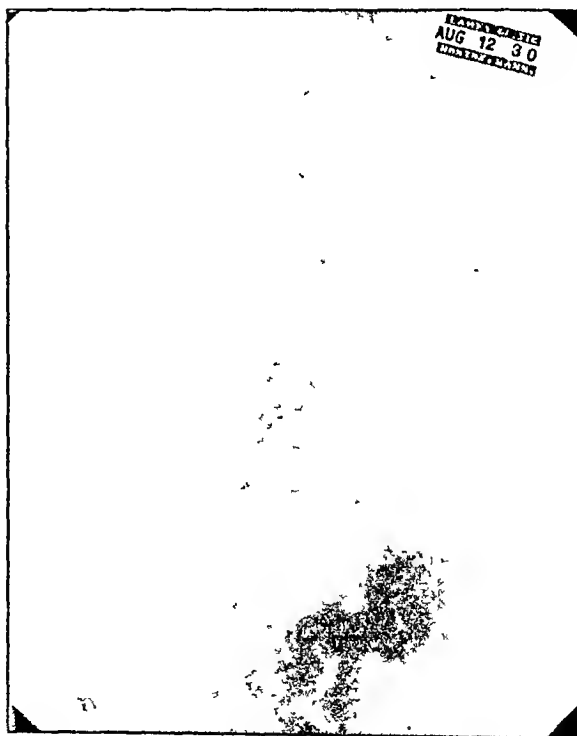


Fig. 4—Case 3

from occasional regurgitation of undigested food when she was nervous or upset.

Physical examination revealed that the patient was obese with marked arteriosclerosis, but no other abnormal findings. Erythrocytes numbered 4,750,000. The value for the hemoglobin was 80 per cent. Gastric analysis revealed the free hydrochloric acid to be 21. On roentgenologic examination after a barium meal a short esophagus was found with a diaphragmatic hernia involving about one-

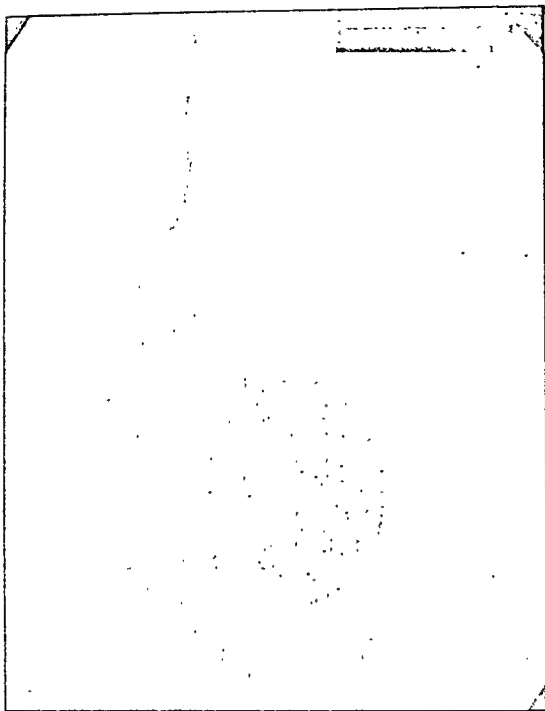


Fig. 5—Case 4

eighth of the stomach above the diaphragm (Fig. 2). On esophagoscopy, a short, dilated esophagus was seen and, at the junction of the esophagus with the stomach, a superficial ulceration, 2 by 1 cm., was made out. At biopsy, chronic inflammation was found. The patient was placed on ulcer management and did well for one year. She then had a hemorrhage and died in December, 1934.

Case 3. A man, aged seventy-five, entered the clinic on June 26, 1930, with a chief complaint of dysphagia of two and a half years' duration. For the past two and a half years he had been unable to eat anything but soft foods because solids caused substernal pressure which was almost unbearable for one to four hours following ingestion. He occasionally regurgitated mouthfuls of undigested food.

Physical examination revealed that the patient was undernourished, with limited diaphragmatic excursion and some emphysema, but no other abnormality. Erythrocytes numbered 3,780,000; the value for the hemoglobin was 60 per cent. Gastric analysis revealed free hydrochloric acid of 80. On roentgenologic examination after a barium meal a diaphragmatic hernia was found above which the esophagus was narrowed for about a third of its length (Fig. 3). Esophagoscopy revealed a narrow fibrous stricture above the junction of the stomach with the esophagus, with a bleeding area on the posterior wall. This patient was placed on ulcer management with relief of symptoms and, with occasional dilatation, did well.

Case 4. A woman, aged sixty-six, was admitted to the clinic on February 1, 1937, with a chief complaint of regurgitation of food of fifteen months' duration. For the past fifteen months this patient had had frequent attacks of subxiphoid pain of a griping nature, accompanied by regurgitation of undigested food, without nausea or retching. After she regurgitated, the spasm disappeared and she could return and eat.

Physical examination was essentially negative. On laboratory examination, the erythrocytes numbered 4,100,-

000 and the value for the hemoglobin was 76 per cent. Free acid on her first examination was negative. Gastric analysis done at the time of esophagoscopy revealed the free hydrochloric acid to be 35. On roentgenologic examination after a barium meal a short esophagus, considerable cardiospasm and irregular dilatation of the lower end of the esophagus were found (Fig. 4). On esophagoscopy, a short esophagus was seen. There was an ulcer on the right side at the lower end of the esophagus, with scarring and narrowing of this portion. At biopsy, aberrant gastric mucosa was found. She was placed on ulcer management with occasional dilatation and did very well.

Case 5. A man, aged fifty-six, entered the clinic on January 15, 1935, with a chief complaint of indigestion of eight years' duration. For the past eight years he had had typical ulcer symptoms, consisting of epigastric pain coming on an hour to an hour and a half following meals, relieved by food or soda, and occasionally awakening him at night. In December, 1932, he had had a severe gastric hemorrhage after which he had been in bed for one week. In April, 1933, he again had vomited blood and this time was placed on a Sippy regime. He had recurrence of pain in 1934. At no time was an ulcer demonstrated. In August, 1934, he began to vomit a few mouthfuls of food occasionally after which he could eat a full meal undisturbed.

Physical examination gave essentially negative results. On laboratory examination the erythrocytes numbered 5,340,000; the value for the hemoglobin was 95 per cent. Gastric analysis showed the free hydrochloric acid to be 23. Roentgenologic examination revealed an irregular constriction of the lower third of the esophagus (Fig. 5). Esophagoscopy showed a short esophagus with an ulceration (2 inches) on the left anterior wall at the junction of the stomach with the diaphragm. Two inches of the stomach were above the diaphragm. This patient was placed on ulcer management and dilatation was performed, but without relief. Finally a phrenicectomy was done after

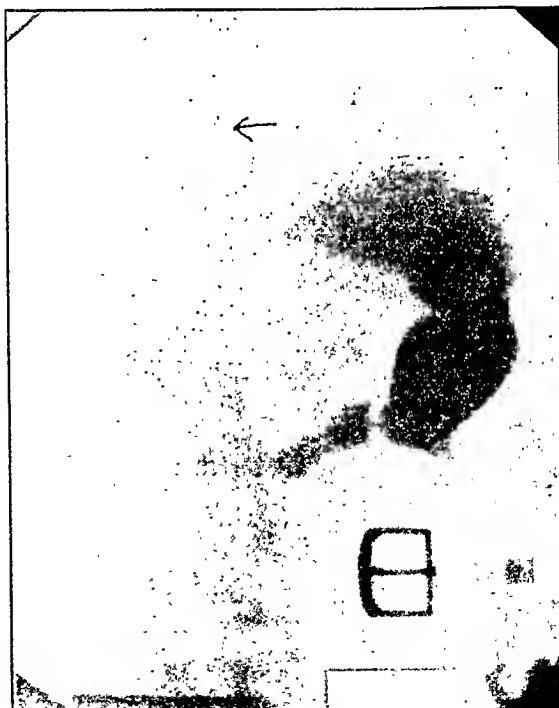


Fig. 6—Case 5

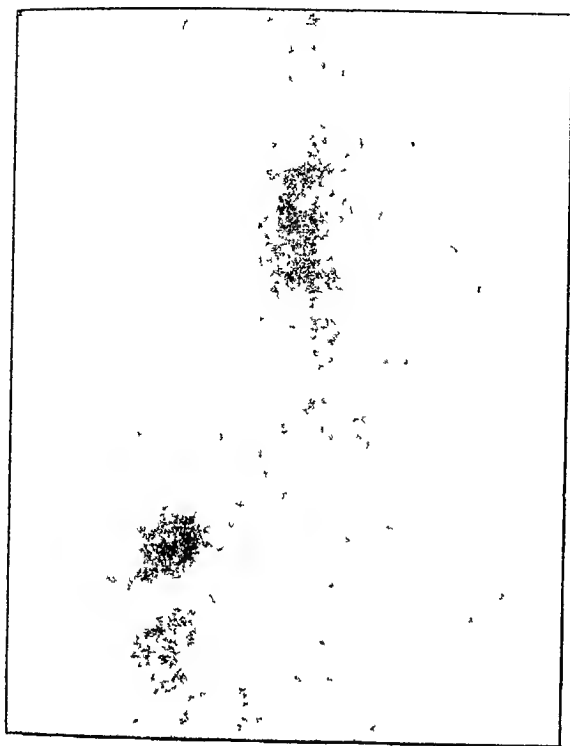


Fig. 7—Case 6

which beginning healing was found on esophagoscopy done a month later. Ulcer management was continued. A roentgenogram on October 14, 1935, revealed a smooth constriction without any hesitation in the passage of the meal. On his last visit to the clinic, October 31, 1936, he had no complaints.

Case 6. A man, aged seventy-five, was admitted to the clinic on March 25, 1932, with a chief complaint of intermittent dysphagia of two years' duration. For two years previous to his admission he had had a pressure sensation in his epigastrium, coming on when he sat down to eat. Until considerable mucus had been regurgitated he had epigastric distress and could not get any water into his stomach. He had never had night distress or typical ulcer symptoms.

Physical examination revealed a mild parkinsonism, bilateral inguinal hernia and, except for the evidence of arteriosclerosis, gave otherwise negative results. On laboratory examination the blood and urine were normal. Gastric analysis revealed the free hydrochloric acid to be 20. Roentgenologic examination of the esophagus showed a dilatation of the upper three-fourths of the length, and a narrowing for 2 inches above the cardia (Fig. 6). On esophagoscopy, a narrowed firm stricture was found, resembling scar tissue, at the lower end of the esophagus. The mucosa below this was gastric. There was a small granulation on the anterior aspect of the stricture. At biopsy, aberrant gastric mucosa was found. He was given a bland diet, alkaline powders three times a day and, when necessary, dilatations were performed at frequent intervals for two years. On his last visit to the clinic, July 14, 1934, he had no difficulty whatsoever.

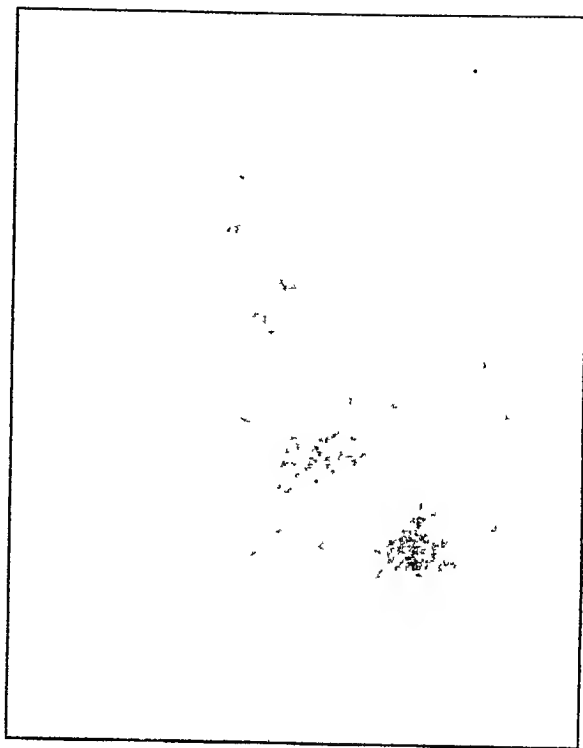


Fig. 8—Case 7

Case 7. A woman, aged sixty, was admitted to the clinic on January 10, 1938, with a chief complaint of difficulty in swallowing of two years' duration. For two years previous to her admission, the patient complained of a sense of obstruction in the esophagus whenever she swallowed her food. A bolus would produce choking and regurgitation of food. At first it occurred at every meal; later it was found that by eating slowly and taking soft foods she experienced no difficulty. She had no indigestion nor associated pain, and only occasional belching.

Physical examination gave essentially negative results. The erythrocytes numbered 4,360,000; the value for the hemoglobin was 85 per cent. Gastric analysis showed a free hydrochloric acid of 36. Roentgenologic examination of the esophagus showed it to be normal down to a point 1 inches above the diaphragm. From this point to the diaphragm the esophagus was narrowed and had an irregular outline. The films suggested a small, penetrating lesion was present. The stomach was normal (Fig. 7). On esophagoscopy, a narrowing of the esophagus was found 2 inches above the cardia. There was no evidence of a fresh ulcer but it was felt that the stricture was due to an old ulcer. The patient was given a bland diet and dilatation was performed twice. To date she has been free from symptoms.

SUMMARY

1. An etiologic factor in the production of peptic ulcer of the esophagus, previously overlooked, is noted.
2. Certain diagnostic criteria are suggested.
3. Seven cases are reported.

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Food Allergy and its Rationalization*

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RECENT papers in this Journal and elsewhere (1, 2, 3, 4) have advocated the therapeutic use of pancreatic enzyme preparations for food allergies. By way of rationalization, an entirely new physiology of digestion has also been proposed.

It is not our purpose to question the clinical observations. The final appraisal of any therapeutic measure must be made by clinicians and will depend wholly on clinical observation. The suggestion that certain allergic cases clear up as their digestive deficiencies are improved is not a new one (5), and has never been in conflict with well-established physiological data. We believe the fallacies involved in the proposed new theory of digestion should not go unchallenged.

Briefly stated, the papers of Oelgoetz *et al* assert that the major functions of digestion are carried on in the blood stream. "The gastro-intestinal tract is essentially a receiving, mixing and eliminating organ." In it the food materials combine with amylase, lipase, and trypsin, and in this form are absorbed, along with any excess of free enzymes. The food materials are then digested in the blood to harmless end-products. When pancreatic secretion is deficient, there is subnormal enzyme concentration in the blood stream and digestion there is delayed. Tissue cells are thus exposed to toxic intermediate protein fragments, and the symptoms of allergy develop. Excess enzymes are not found in the blood, but are stored in the tissue cells—which are unable to provide their own. Enzyme concentration in the tissues is exactly one hundred times that of blood. Brain and heart, however, are said to have no enzymes. In blood, lipase, amylase, and trypsin are present at a fixed level and in parallel concentrations, so that measuring one of them is equivalent to measuring all. In allergies, the blood enzyme level is low because of inadequate pancreatic secretion, and this may be corrected by feeding active pancreatic preparations. A test is recommended for determining the functional adequacy of the pancreas, which depends upon the decolorization of starch iodide by serum, and is said to be a test for amylase. Evidence

is claimed for the automatic control of pancreatic secretion by the enzyme level in the blood.

In the following paragraphs we propose to examine critically some of the more striking assertions advanced by Oelgoetz and the evidence upon which they rest.

What is the evidence for massive absorption of undigested foods as a preliminary to digestion in the blood? There is none. Walzer's work is referred to (6) as authority for such a conclusion. What it actually proved, however, was that normal persons as well as allergic ones frequently show traces of absorbed food proteins in the blood. The success of Walzer's experiment depended on the most delicate test yet devised for protein, and objectively demonstrated in the normal person, what the allergic symptoms had long made clear in the highly sensitive individual. The primary fallacy here is the assumption that a minute trace of food antigen absorbed, proves that the entire meal is thus absorbed. Oelgoetz states specifically that alkali albuminate is absorbed and is present in the blood stream. But it has never been found there by Oelgoetz or anyone else.

Verzár's work (7) indicates that undigested fats are not absorbed.

Starch is easily detected by a delicate color reaction, and if absorbed as such would constitute evidence in favor of Oelgoetz's assumption. It has never been found in the blood.

There evidently is no factual basis for the assumption of extensive food absorption.

What evidence for digestion taking place in the blood stream? The presence of the enzymes lipase, amylase, and proteinase.

What evidence that these are derived from pancreatic juice? Their specific origin has not been well established. They may indeed come from the pancreas either directly, or by absorption of pancreatic juice. The recent work of Crandall, Comfort and Osterberg (8, 9, 10) relates high serum lipase with pancreatic pathology. The enzymes may also be derived from leucocytes.

Of what significance are these enzymes? In Oelgoetz's hypothesis, the only enzyme of significance in food allergies is trypsin, and to be of significance it

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must be present in concentrations adequate to account for the rapid digestion of food proteins. All the data indicates clearly that trypsinase is present in traces only. If the food proteins were extensively absorbed, as Oelgoetz asserts, their digestion in the blood would be a very prolonged process.

On the other hand, the evidence presented by Folin (11) and by Van Slyke (12) in 1912 makes it perfectly clear that the digestion of protein in the intestine is rapid and relatively complete, and that the products of such digestion, the amino-acids, are the materials absorbed. There is nothing in this statement, however, to preclude the absorption of such traces of unaltered or partially digested protein material, as Walzer has demonstrated.

What evidence is there that the tissues must be supplied with their hydrolytic enzymes from pancreatic secretion? No direct evidence has ever been produced. Boldyreff (13) originally advanced this hypothesis to account for the disappearance of pancreatic enzymes from the intestine. No tissue enzyme studies were made by Boldyreff, though confirmation appeared at hand in some of the older literature. We have pointed out (14) that the interpretation of this older literature is hazardous, inasmuch as there was no control of the pH of digests at that time, and the characterization of trypsin was necessarily vague. Our own experimentation has failed to indicate trypsin in tissues in more than traces. The typical proteinase of mammalian tissues is cathepsin. Where a trypsinase has been found, it appears referable to the leucocytes (15).

It would be difficult to explain Oelgoetz's statement that heart and brain do not contain the usual tissue enzymes. So far as proteolytic activity is concerned, they have been shown to resemble other tissues (16, 17).

Another unfounded statement is that tissues—other than brain and heart—contain "the serum enzymes in a concentration exactly one hundred times of that of serum." Considering the difficulty in demonstrating even a trace of a trypsinase in liver or muscle, this should make protein digestion in the blood highly problematical.

What evidence is there that feeding pancreatic enzymes leads to their storage in the tissues? Oelgoetz states that feeding a commercial trypsin preparation to rabbits for a week led to doubling liver trypsin and increasing that of the spleen seventeenfold. We have repeated this experiment on 19 rabbits fed for periods ranging from one to six weeks with the same pancreatic preparation recommended by Oelgoetz. Liver, spleen, kidneys and muscle tissue were examined by standard technique (14) for trypsin. Traces of an enzyme acting at pH 7-8 were usually detected. There was no more in the experimental animals than in the controls. We therefore have been unable to confirm the results reported by Oelgoetz.

HOW IS PANCREATIC HYPOFUNCTION DIAGNOSED?

No direct attempt to correlate blood enzyme and pancreatic secretion has been made by Oelgoetz. Instead he describes a test for amylase, and assumes the other enzymes are invariably comparable in concentration to it in the blood. The test is an interesting but crude measure of iodine absorption by the serum. Actually it is not a test for amylase—since the digestion of starch is not measured, and amylase, in

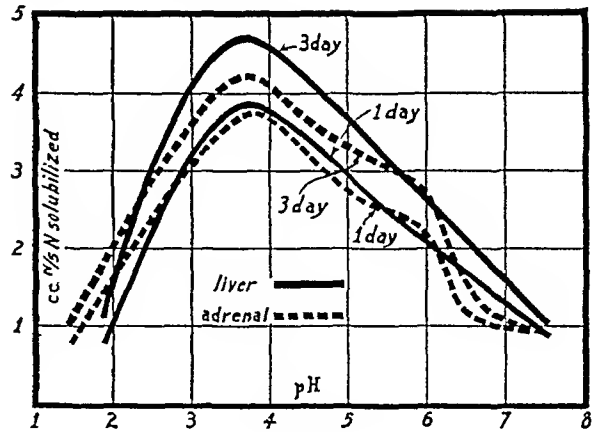


Fig. 1

fact, does not give it. Many other compounds unrelated to amylase do. In the serum, such reducing agents as glutathione, and ascorbic acid will take up iodine, and so contribute to the test. Whether the test measures pancreatic function or not has never been determined. All that can be said of it now is that it is not a test for amylase, and that its significance remains to be determined.

What evidence is there for believing the three enzymes described in blood are invariably present in comparable amounts? Oelgoetz presents a table of figures which show absolutely no variation in the hourly samples assayed for amylase, lipase, and trypsin. Considering the methods used, we must frankly question the reliability of the results. The wide variations recorded by Crandall, Comfort and Osterberg (8, 9, 10) for lipase may be cited as reliable evidence against such constancy as Oelgoetz describes. Boldyreff (13) also found very considerable fluctuations in the blood enzyme concentrations. It might further be pointed out that such constancy of enzyme level, regardless of time of day or ingestion of meals, would itself cast serious doubt on the intestinal origin of the enzymes.

In concluding this discussion, we should like to present in graphic form the proteolytic activity of tissues like liver and adrenals. The experimental details are in press elsewhere (18) and need not concern us here, other than to say the methods used for obtaining the results are recognized as quantitative and reliable.

It will be noted that protein is rapidly and extensively digested at a pH 3 to 4. This is typical of mammalian tissues—including brain and heart—and indicates the enzyme cathepsin. At a pH of 7.5 adrenal gland tissue shows no measurable digestion, although this is close to the optimum reaction for trypsin. We conclude there is no detectable trypsinase present. In the liver, we find a trace of proteolysis at pH 7.5, and we assume there may be a trace of trypsinase. The data does not prove it, since it may be due to the ereptic enzymes known to be present, acting on large molecular protein fragments already present in the tissue at the moment of death, or produced by cathepsin during the preparation of the digests. If we were able to characterize this enzyme more sharply as a trypsinase, the data still does not indicate whether it is derived from pancreas, or as is more probable, from

leucocytes lodged in the gland. The experiment does show how extremely small the activity is which Oelgoetz describes as being 100 times that of the blood.

Finally it may be stated that there is nothing in the soundly based facts of the physiology of digestion which is difficult to reconcile with clinical success in the use of pancreatic enzymes. It is obvious that a deficient digestive mechanism will be slow in the

cleavage of protein, and so may increase the chances of antigenic molecules getting into the blood stream from the intestine. When the clinical evidence establishes the fact of therapeutic value, there will be no difficulty in providing a rational explanation of the observation. In the meantime a hypothesis which ignores established facts, and substitutes assertion for trustworthy evidence should not be taken too seriously.

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Pain In Carcinoma of the Stomach: Preliminary Report

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PAIN is one of the most frequent symptoms of intra-abdominal pathologic conditions. Curiously and unfortunately, it is one of the least understood of all of the manifestations of disease. Many of the problems relative to pain will be clarified not by the study of laboratory findings, but rather by the study of data obtained through careful evaluation and correlation of the painful experiences of patients with inspection of the lesions which actually had been responsible for these symptoms. Thus, information of academic importance as well as of clinical usefulness may become available. In the hope that some such information might be obtained, we undertook to study a large series of cases of carcinoma of the stomach. Only such cases were accepted for study in which carefully taken histories were available, fairly definite localization of pain occurred and the nature and extent of the pathologic process had been studied at the time of laparotomy or necropsy. Unfortunately, patients who have carcinoma of the stomach often present themselves for the first time with all of the evidence of a lesion which has progressed to the state of inoperability. In some cases, no evidence of the presence of this disease was available from the history alone.

We are reminded of the instance of one woman who, during the course of routine physical examination, insisted on having a roentgenologic examination of

her stomach performed because she had "a hunch that there might be something wrong there." Roentgenologic examination, in this case, gave evidence of rather extensive carcinoma of the stomach but, even after this information was available, neither were we able to elicit any definite symptoms suggesting the presence of this disease, nor did physical examination in any way suggest abdominal malignancy.

In this paper, it is our intention to discuss briefly a few types of malignant lesions that involve the stomach and to consider how carcinoma of this organ might be productive of the symptom of pain. Before proceeding to the discussion of the mechanics of the production of pain in cases of gastric malignancy, it might be well to review briefly some of the pathways which can be taken by such impulses traveling between the stomach and the patient's consciousness.

PATHWAYS OF PAIN CONDUCTION FROM THE STOMACH

Painful impulses arising in the stomach may originate in the wall of the organ, pass along the sensory bundles in the sheaths of the splanchnic nerves, cross through the white rami communicantes of the thoracic nerves along the posterior roots, and thus reach the posterior horn of the spinal cord. Pain also may be projected to the spinal cord over the sensitive cerebrospinal somatic nerves, branches of which supply the parietal peritoneum, the mesentery of the bowel

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and the retroperitoneal tissues. If lesions involve the upper portion of the stomach, some impulses undoubtedly reach the central nervous system through the phrenic nerves. There are several other pathways which may be of some slight importance; these are the ganglionated sympathetic chain or the aortic plexuses from which impulses may reach the spinal cord through the rami communicantes. In all probability, the three more important pathways of conduction are the splanchnic nerves, the sensitive cerebrospinal somatic nerves, and, in cases of very high gastric lesions, the phrenic nerves.

MECHANICS OF PRODUCTION OF PAIN BY GASTRO-DUODENAL LESIONS

It is important to have some conception of the mechanisms involved in the production of pain caused by lesions involving the stomach and it should be mentioned here that there are still many unexplainable phenomena relative to this subject. The discussion of pain arising from involuntary organs demands the consideration of certain fundamental biologic phenomena relative to the phylogenetic development of the nervous system as a whole. In order to evoke the appropriate responses to varying external environmental changes, the surface of the body is endowed with end organs receptive to certain special types of stimuli acting on the body from without. The stimulus evokes a sensation which reaches the brain through afferent nerve fibers. Each type of sensation has its own afferent system of nerve fibers coursing along well known paths in the central nervous system. A stimulus mediating the sensation of pain, then, enables the organism to respond appropriately by carrying out a defensive reaction, the character of which depends on the source and seriousness of the painful stimulus. Similarly, in order to evoke the appropriate responses to varying internal environmental changes, the alimentary canal is endowed with an afferent "pick-up" system receptive, in turn, to certain special types of stimuli to which its environment exposes it. A stimulus mediating the sensation of pain again spells a threat to its integrity and evokes responses accordingly. It is obvious, however, that the high degree of specialization involved will make the stimuli which are adequate for the production of pain on the surfaces of the body more or less meaningless when operative on the gastro-intestinal tract. Tactile sensibility is entirely lacking in the viscera and thermal sensibility is almost lacking; pain cannot be produced by pinching or cutting the abdominal viscera. The presence of disease, however, by causing a disturbance of the function of the organ concerned does supply the adequate stimulus to evoke a sensation which the higher cerebral centers interpret as pain. It is important to realize that sensations resulting from the normal physiologic processes of the stomach are relayed through the same pick-up system to the central nervous system but the sensations so evoked fail to reach the discriminative cortical centers of the brain unless the stimulus is unduly strong, when it again becomes adequate to evoke subjective appreciation.

The adequate stimulus is assumed to be an increase in pressure within gastro-intestinal segments, which results from stretching or contraction of the circular fibers of the viscus. It has been suggested that, in the stomach, this spasm can be the result of hyperacidity which acts as a trigger mechanism that sets in motion

spasm which, in turn, may constitute a stimulus entirely adequate to be appreciated as pain. Furthermore, stretching of muscles or contracting fiber could be incident to bombardment of peristaltic waves against an obstructing or partially obstructing segment anywhere in the bowel. This could be caused by organic obstruction or by functional or sphincteric spasm of any circular muscle.

It is apparent that when lesions progress beyond the confines of the intestine and invade neighboring tissues which are innervated by branches of the spinal sensory nerves, the stimulus adequate to provoke a sensation of pain will be the same stimulus adequate in other regions of the body similarly innervated. Dragging on a mesentery will evoke a painful response, for the same reason.

One of us (1) studied a large series of surgically verified peptic ulcers in order to ascertain the behavior of pain under various histopathologic conditions. This study revealed that a clearly defined uncomplicated ulcer produces diffuse epigastric distress, a purely visceral phenomenon manifesting itself over splanchnic paths only. Obstructing lesions associated with vigorous peristaltic activity produce the familiar colicky pain which again is splanchnic in nature and is felt diffusely in the epigastric region. With invasion in the progress of perforation of the tissues surrounding the wall inhabited by peptic ulcer, it seems to us that the warnings of the traumatizing effect of such invasion would be conducted over the somatic nerves guarding these tissues. Since these nerves are sensitive to many stimuli in addition to the adequate stimulus producing pain along the splanchnic route, a syndrome less rhythmic and less clearly defined than the syndrome caused by uncomplicated ulcer will be produced. Thus, we felt that disturbed syndrome of ulcer, that is, one in which the symptoms are mainly or wholly carried by the somatic nerves, easily could be assumed to have received the predominance of impulses arising outside the wall of the bowel over branches from this system of nerves; whereas, reception of sensations over the plexuses of the splanchnic nerve not distracted by a mixture of impulses arising over the somatic nerves conceivably might be assumed to produce the pain-food-ease sequence so characteristic of uncomplicated duodenal ulcer.

In cases of perforating peptic ulcer a shift of pain from its original site into secondary regions was noted frequently. In cases of duodenal ulcer the characteristic shift of pain was toward the right costal margin; in cases of gastric ulcer, this was usually toward the left costal margin; in cases of jejunal ulcer, the most frequent secondary region of invasion was to the left and along the umbilicus, even extending as far as the inguinal regions. Morley (2) interprets this behavior of pain as the result of impulses received by the sensory spinal nerves and transmitted to the superficial branches of such nerves. This shifting distress he classifies as "referred pain." Regarding the origin of such pains, he stated that "referred pain only arises from irritation of nerves which are sensitive to those stimuli that produce pain when applied to the surface of the body." He assumed that tissues such as the mesentery, mesocolon, and abdominal wall are innervated by the sensory spinal nerves, a presumption which clinical experience would lead us to assume to be entirely reasonable.

THE PHYSIOLOGY OF PAIN AS APPLIED TO CARCINOMA OF THE STOMACH

Palmer (3), in discussing the various factors which he felt entered into the production of pain in cases of carcinoma of the stomach, thought them to be irritation of the pain-producing mechanism by acid, tension of muscles, and, probably, malignant infiltration of the nerve fibers. We believe that the painful symptoms of carcinoma of the stomach utilize for their interpretation conduction pathways and mechanics of the production of pain similar to those which produce pain in cases of peptic ulcer and in cases of lesions of the bowel generally. We can see no pathologic or physiologic reason why this should not be so, and clinical study of a large series of cases of carcinoma of the stomach would seem to bear out the assumption.

The two important methods of the production of pain then would be, first, visceral phenomena utilizing the splanchnic pathway and requiring an adequate stimulus and, second, somatic phenomena which would utilize the spinal sensory group of nerves and requiring only the pain-producing mechanism productive of distress of the surfaces of the body. In order to assume a visceral phenomenon, it would be necessary to postulate stretching or contraction of the muscular fibers within the gastric wall. In the case of ulcers, it is probable that acidity is one of the trigger mechanisms which sets this in motion. Because acidity is frequently low or absent in cases of carcinoma of the stomach, it is clear that the splanchnic phenomenon which otherwise might become a manifestation of this disease probably would be absent. In other instances, particularly those in which acidity is adequate, the distress of carcinoma is indistinguishable from that produced by peptic ulcer. Relief is obtained in the same way and the pain often originates some time following meals, as it does often in cases of benign gastric or duodenal ulcer. This, in all probability, is a visceral phenomenon.

Occasionally, carcinoma of the stomach is productive of gastric retention. This may be owing to several causes, such as actual obstruction at the pylorus or secondary pylorospasm related to lesions anywhere in the stomach. This, again, would be a splanchnic phenomenon which might arise at any time during the digestive cycle.

With the extensive invasion of the gastric wall and perigastric tissues by progression of the malignant lesion, somatic pathways would be invaded. In such instances, pain can be produced even though the adequate stimulus required to initiate the splanchnic phenomenon were lacking originally. It seems particularly noticeable that, when there is evidence of an inflammatory reaction in addition to that of malignancy, such lesions produce more severe pain which includes tenderness and, often a shift of pain into secondary regions, as well as pain occurring at night. On the other hand, it can be seen readily how carcinoma of the stomach might progress to a very serious degree before either the splanchnic or somatic mechanisms of production of pain could be set in motion. The shift of pain into the left shoulder and neck would be the result of a direct invasion of tissue innervated by the phrenic nerve.

SUBDIVISION OF MATERIAL FOR STUDY

In reviewing the histories of the cases under con-

sideration, we tried to subdivide these into several groups. This was done in order to place in separate categories, as much as possible, histories of cases in which similar characteristics regarding symptomatology or pathology were apparent. Group 1 contained cases in which lesions usually were diffuse but were nonpenetrating and nonobstructing. Pain was notably absent. Group 2 contained cases in which lesions were associated with obstruction. Group 3 contained cases in which the lesions were penetrating. This group was subdivided as follows: (a) cases associated with normal or high levels of gastric activity, presenting pain often indistinguishable from that of benign penetrating lesions; (b) cases associated with an inflammatory reaction surrounding the lesion with or without the presence of free hydrochloric acid, and (c) cases without inflammation in the region of the lesion and with low acidity or none. Pain usually was mild or absent. Group 4 contained cases of miscellaneous lesions not classified in the above subdivisions. In a subsequent publication these various types will be considered in greater detail.

REPORTS OF ILLUSTRATIVE CASES

Case history illustrating group 1. Until two months prior to coming to the clinic, this patient had been considered perfectly well. Lately, he had lost weight and strength. Except for vague epigastric distress after eating and marked anorexia there were no other digestive disturbances. The total gastric acidity was 8; hydrochloric acid was absent. Roentgenologic examination revealed extensive carcinoma of the stomach.

At exploration, there was a huge, irregular tumor just proximal to the pylorus, extending along the lesser curvature to the cardia. About the only region not involved was a small portion along the greater curvature at the cardia. Metastatic lesions were not discoverable at operation.

Except for the systemic manifestations this patient had but little to suggest serious organic disease. The vague epigastric distress and the anorexia might well have been of no serious significance. In this case, there was an absence of free hydrochloric acid so that the trigger mechanism which might result in gastric spasm was absent. There was no appreciable inflammatory reaction surrounding the lesion and no obstruction. In this case, therefore, neither somatic nor splanchnic mechanisms of pain would seem to be seriously involved and, consequently, there might well be no local manifestations of the disease. Unfortunately, this type frequently proceeds to the stage of inoperability without the production of any local symptoms.

Case history illustrating group 2. A man, aged sixty-eight years, had lost weight, strength and appetite gradually for a year and a half. Five months prior to examination at the clinic, he had diarrhea for four or five days. For three weeks prior to registration, he complained of gripping midepigastrie pain which was not projected in any direction commencing an hour and a half after meals and relieved by vomiting. The material vomited at times contained food eaten the day before. Nausea and anorexia had become very marked in this period. The total gastric acidity was 36. Free hydrochloric acid was present. One thousand cubic centimeters of gastric contents were recovered by intubation. There was roentgenologic evidence of dilatation of the stomach and obstruction of its outlet.

At operation, carcinoma was found at the pylorus causing obstruction of the outlet of the stomach. Metastasis had occurred to lymph nodes (adenocarcinoma grade 3 on the basis of 1 to 4), but the stomach was freely movable.

This case seems to illustrate a splanchnic type of phenomenon which might be set in motion by any obstruction of the outlet of the stomach. With interference to the normal peristaltic movements, bombardment against the closed pylorus might readily be assumed to produce increased tension or constriction of circular fibers in the wall of the stomach sufficient to produce symptoms. Because of early production of distress and because of the fact that these lesions frequently involve the pyloric region, the degree of operability is usually quite high.

Case history illustrating group 3 (a). A man, aged thirty-nine years, had symptoms dating back three months. He complained of gas and a localized region of epigastric pain the size of a dollar. This pain was projected upward from this region into the thorax, particularly the left side. The pain commenced two hours after meals and was relieved by food and soda. He was awakened by it usually around midnight and again around two o'clock in the morning. Eating eased the pain promptly. There was partial relief when he restricted his diet. The total gastric acidity was 80 and free hydrochloric acid, 68. There was an ulcerating lesion on the posterior wall of the greater curvature on roentgenologic examination.

At operation, a mass 10 by 12.5 cm. was found on the posterior wall of the middle third of the greater curvature; the mass had perforated the transverse mesocolon, requiring excision of part of the large bowel. Partial gastrectomy was performed. Pathologic examination of one of the nodes gave evidence of carcinomatous involvement. Following his discharge, he never regained his strength. Three months later, after an enema, severe hypogastric pain developed, with generalized abdominal soreness and fever. He returned for further examination at which time a diagnosis of generalized peritonitis was made. Meanwhile, a lymph node had become apparent in his axilla which, on biopsy, was found to be carcinoma, grade 4.

The dual mechanism of the production of pain is illustrated equally well in this case. The penetrating features are predictable by the nature of the pain and its characteristic radiation into secondary regions. The gastric acidity was high. In addition to the usual pattern of somatic pain, there is the episode of acute perforation with involvement of the peritoneum and its associated clinical picture.

Case history illustrating group 3 (b). A man, aged fifty-nine years, had symptoms for only one month. These consisted of epigastric pain especially at eleven o'clock in the morning and at four o'clock in the afternoon; partial relief was obtained by taking soda. When severe, the pain was projected through the body to the inferior angle of the right scapula. There was considerable loss of weight and strength. The total gastric acidity was 32, free hydrochloric acid 20. Roentgenologic examination gave evidence of a perforating gastric ulcer on the lesser curvature. At operation, a crater 2.5 cm. in diameter was found, associated with much inflammatory reaction surrounding the ulcer. On pathologic examination it was found to be carcinoma without any apparent involvement of lymph nodes.

This case illustrates adequately the dual mechanism of production of pain similar to that so frequently encountered in cases of penetrating benign lesions of the stomach. First, there is the usual splanchnic syndrome characterized by diffuse epigastric distress commencing late after meals but relieved by food or soda. Second, there is the somatic syndrome resulting from invasion of contiguous tissues innervated by the spinal sensory nerves. The shift of pain into the

region of the right scapula, in all probability is owing to projection of painful sensations along the entire distribution of the particular spinal sensory nerves invaded by the inflammatory reaction surrounding the ulcer. We have, in our series, parallel instances, but with anacidity, in which an inflammatory reaction in regions innervated by the somatic system produced similar symptomatology.

Case history illustrating group 3 (c). A woman, aged sixty-five years, never had experienced abdominal pain except for "soreness of the bowels" of three months' duration and a sense of fullness after a large meal. The total gastric acidity was 20, and free hydrochloric acid was not present. Roentgenologic examination gave evidence of a carcinomatous ulcer on the lesser curvature involving the lower half of the stomach.

At operation, the cancer was found to have perforated into the pancreas and considerable dissection of the pancreas was required to remove the lymph nodes and lesions. Pathologically, it was small cell carcinoma and, above the ulcer, there was a malignant adenomatous polyp. The lymph nodes were not involved.

This case stands in rather interesting contrast to the previous penetrative lesions, in that pain was very much in the background despite quite considerable penetration into adjoining viscera. It can be assumed that all of the factors necessary to condition the adequate stimulus were not present and it can be affirmed rather strongly that acidity is one of those factors.

SUMMARY

In this paper we have attempted to outline in a general way the important pathways of conduction of pain from, and mechanics of production of pain in, the viscera in the upper part of the abdomen. The general principles involved follow a pattern similar to that encountered in cases of benign lesions of the stomach. We felt that, if gastric carcinoma superficially invades the tissues of the stomach and results in disturbances of its normal mechanics, pain may result. This pain would utilize pathways coursing along the splanchnic vessels. In order to be interpreted as pain, these irregularities in mechanics would require an "adequate" stimulus which, in this case, would be spasm or obstruction. If, on the other hand, the lesion burrows through the gastric wall into the tissues surrounding the organ, pain would be relayed to the spinal cord over the spinal sensory group of nerves and, in this instance, wide distribution and reference of pain may be produced. If the lesion invades the regions of the distribution of the phrenic nerve, pain will be referred into the left side of the thorax and to the "peripheral distribution" of this nerve which would be into the left shoulder and the base of the neck. Such a lesion is usually inoperable. Any stimulus which would initiate the sensation of pain on surfaces of the body also could produce pain in penetrating lesions.

Applying these hypotheses to the problem of pain in cases of cancer of the stomach permits an explanation of the apparent paradoxical behavior of distress among patients harboring such lesions. Who, at operation or necropsy has not viewed with surprise tremendous cancers involving most of the stomach which have produced no pain whatsoever? After all, this should be no more the cause of astonishment than to witness surgical procedures on the stomach which caused patients no pain even though only local anesthesia was used. The mechanisms which produce pain in such cases depend on the production of an adequate

stimulus, such as stretching or constriction of the circular muscular fibers which would require a mechanical disturbance, such as spasm or obstruction. If cancer does not set in motion this adequate stimulus, it is likely to produce no pain whatsoever. If, on the other hand, there is mechanical disturbance such as interference with normal emptying or invasion of the pylorus, pain or at least a sense of epigastric distress is likely to be one of the earlier manifestations of this disease.

Cancer of the pylorus therefore is more often amenable to surgical treatment than are other types of cancer, not only because of its resectability from a physical standpoint but because of the fact that, as a rule, it produces symptoms relatively early. Shift of pain from original to secondary regions among patients who have cancer of the stomach is of varying significance. In the event that the lesion is small, for instance, a penetrating peptic ulcer harboring in its depth malignant degeneration associated with hyperacidity, a shift of pain may not be of very serious significance. If, on the other hand, the lesion is fairly extensive and the patient complains of shifts of pain from the original into secondary regions, the lesion will be found to be inoperable in almost all instances. This, of course, is owing to the fact that cancer has penetrated the wall of the organ and has invaded tissues contiguous to the stomach. The shift of pain, in such instances, is owing to invasion of the spinal sensory nerves.

In a general way, it can be said that cancer of the stomach in which gastric chemistry is normal or is elevated is much more likely to produce a painful

syndrome than that in which there is no acidity or only a trivial amount of hydrochloric acid. This is probably owing to the fact that the acid acts, as it does in cases of benign gastric lesions, as a trigger mechanism which initiates spasm and this, in turn, is responsible for the sensation of pain. Otherwise stated, with the exception of pyloric lesions which cause early obstruction, the presence of carcinoma of the stomach is suspected most usually by its complications and its systemic effects when the lesion has advanced beyond the bounds of operability.

CONCLUSIONS

1. Splanchnic phenomena in cases of carcinoma of the stomach do not cause dramatic effects unless obstruction is present. Thus, even extensive cancer of the stomach may not produce pain, particularly if free hydrochloric acid is present in small amounts or is absent.

2. Somatic phenomena are prominent but because they depend on penetration of the lesion beyond the confines of the bowel, symptoms are delayed until such extension has occurred. For this reason cancer associated with pain referred to the thorax or back, or along the distribution of the phrenic nerve is usually inoperable. The presence of either free hydrochloric acid in the gastric contents or an inflammatory reaction in the vicinity of the lesion, or both, may accentuate somatic pain.

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The Effect of Acetyl-B-Methyl Choline (Mecholyl) on the Gastric Secretion in Animals and in Man*

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THE action of acetyl-B-methyl choline chloride (mecholyl) on the gastric secretion was first studied by Abbott (1). He determined the volume and acidity of the gastric secretions in 9 human subjects after mecholyl in dosages of 200 to 300 mgm. orally and 5 to 10 mgm. subcutaneously. In most cases there was a slight to marked increase in acidity and in no instance was there a marked decrease in gastric acidity. There was an increase in acidity in 3 of 6 cases of hypochlorhydria, but he felt that histamine was more useful for this purpose.

Ferguson and Smith (2) were the next investigators to report on the effect of mecholyl on gastric acidity. They reported the abolition of free gastric acidity in monkeys when a sufficiently large dose of

mecholyl was administered subcutaneously. In their cases the total acidity paralleled the free acid curve but the total chlorides were unaffected. The mucous secretions were increased, particularly, the saliva.

Myerson (3) and his co-workers published a report on the changes in gastric secretion in physiologically normal human subjects following the injection of 20 to 30 mgm. of mecholyl subcutaneously. They claimed that there was a "diminution or disappearance of the digestive secretions, hydrochloric acid and pepsinogen, and finally, the appearance of mucin." They reported similar findings with mecholyl by iontophoresis and these observations were recorded in a later communication (4). They felt that Abbott had failed to use sufficiently large doses of mecholyl and thus explained the diametrically opposite results.

Schnedorf and Ivy (5) in a recent publication found that mecholyl caused acid secretion in previously an-

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acidic monkeys. They also reported that these monkeys gave an acid response to histamine after mecholyl injection where they had failed to get such a response before.

It is apparent from these reports that the issue was confused. Two groups of investigators working with monkeys reported opposite effects of mecholyl on gastric secretion; two other groups working with human subjects also disagreed.

In our work on the effect of autonomic drugs on the gall bladder (6) and hepatic secretion (7), we were impressed by the marked mucinous salivary response to mecholyl. This result was obtained in human subjects and cats regardless of whether mecholyl was given by injection or iontophoresis. The gross physical similarity of specimens obtained on gastric or duodenal drainage to the saliva was striking. We also found that anaesthetized cats had a definitely respiratory type of death on certain mecholyl dosages and on postmortem examination the lungs showed the changes characteristic of drowning. These same dosages, however, were readily tolerated if a tracheal cannula was inserted prior to the mecholyl administration. Thus it was obvious that these deaths had been caused by drowning in aspirated saliva and that bronchial secretion and spasm were unimportant factors.

Abbott (1) was the only one of the previous investigators to specifically state that precautions were taken against swallowing saliva. We devised the following experiments to determine what influence swallowed saliva had on the results obtained by other of these investigators.

EXPERIMENTAL FINDINGS

Animal Experiments

Rabbits varying in weight from 2.5 to 3.5 kilograms

were anaesthetized by the intraperitoneal injection of sodium amytal (75 mgm. per kilo.). A tracheal cannula was inserted. A No. 18 Levine tube was passed into the stomach through the mouth in some; through an opening in the portion of the esophagus below the diaphragm in others. In the latter group another tube was passed partially up the esophagus and in some cases a tube passed through the mouth to meet the tube ascending the esophagus. Gastric specimens were collected before and at intervals after the subcutaneous injection of 2 and 4 mgm. of mecholyl. The volume of each specimen was recorded and the free and total acidity determined by titration with .02 N sodium hydroxide using Topfer's reagent and phenolphthalein as indicators. The gastric secretion was continually tested with congo red paper.

Because of the persistent gastric residue in rabbits an accurate determination of the change in gastric secretion was not possible. The gastric secretion was always positive with congo red paper and there was no evidence to suggest the outpouring of alkaline and mucinous gastric secretion in any great amount. A large amount of saliva was secreted into the oral cavity but this did not reach the stomach in the anaesthetized rabbit with or without a tube passing down the esophagus.

Because of residue which was a handicap in the experiments with rabbits the experiments were repeated on cats. Three cats (weight 3 to 3.5 kilograms) were anaesthetized by intraperitoneal injection of sodium amytal (75 mgm. per kilo.). In all three the gastric contents were found to contain no free hydrochloric acid on fasting and the condition persisted after subcutaneous injections of 2, 4 and 10 mgm. of mecholyl.

Human Experiments

A Levine tube was passed in human subjects and each patient placed on his right side. All of the fasting content was aspirated, the quantity noted, and tested with congo red paper for hydrochloric acid. An emesis basin was placed at the side of the patient's mouth and he was urged to expectorate all the saliva and to avoid swallowing.

TABLE I

Data on gastric secretion in human subjects following subcutaneous injection of Acetyl B-Methyl Choline Chloride (Mecholyl). (Two typical cases)

Patient	Patient lying on right side:					P. K. 11/2/37					H. R. 11/26/37					H. R. 12/10/37				
	P. K. 10/22/37																			
	T.	V.	Acid F.	T.*	A.	T.	V.	Acid F.	T.*	A.	T.	V.	Acid F.	T.*	A.	T.	V.	Acid F.	T.*	A.
Fasting		12	36	54	0		10	61	77	0		85	38	50	0		30	64	75	0
Mecholyl		25 mg.					25 mg.					25 mg.					25 mg.			
Spec. 1	0-2	10*	13	26	0	0-2	3	39	53	0	0-7	30	39	51	0	0-3	30	33	45	0
Spec. 2	2-25	67	0	4	40	2-25	75	0	9	54	7-20	45	0	10	0	3-20	45	0	15	23
Spec. 3	25-60	20	38	52	0	25-30	75	36	47	0	20-25	90	98	109	0	20-30	25*	66	77	0
Saliva	60	60		33		30	100		55		25	100		49		30	75			57

Patient	Patient lying on abdomen with mouth rag inserted:					11/10/37					11/27/37					12/8/37				
	10/27/37																			
	T.	V.	Acid F.	T.*	A.	T.	V.	Acid F.	T.*	A.	T.	V.	Acid F.	T.*	A.	T.	V.	Acid F.	T.*	A.
Fasting		30*	53	67	0		25	23	39	0		45	15	30	0		50	61	75	0
Mecholyl		25 mg.					25 mg.					25 mg.					25 mg.			
Spec. 1	0-5	30*	40	54	0	0-10	11	58	73	0	0-10	50	81	97	0	0-7	37*	71	87	0
Spec. 2	5-15	42*	67	81	0	10-20	22	53	66	0	10-25	120	120	132	0	7-20	46	75	84	0
Spec. 3	15-35	33*	56	70	0	20-30	4	88	102	0						20-30	15	95	111	0
Saliva	35	180		56		30	180		52		25	175		57		30	120			61

T—time in minutes after Mecholyl injection.
F—free acid.

T*—total acid.

V—volume in cc.

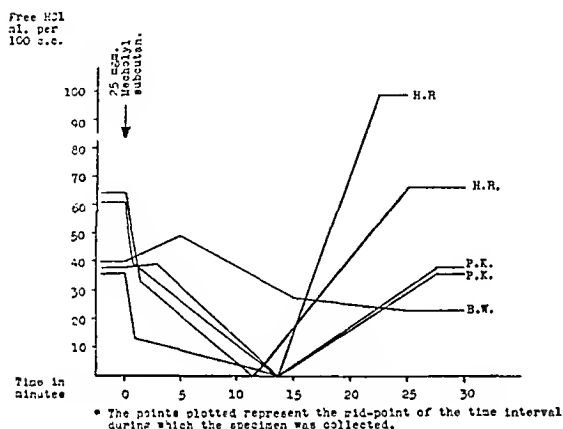
A—% amylase activity.

* bile stained.

Mecholyl 25 mgm. was injected subcutaneously. Constant aspiration was attempted and the contents obtained were continuously tested with congo red paper. The volume of the secretion was recorded at intervals and these speci-

FIG. 1*

EFFECT OF MECHOLYL ON FREE ACIDITY OF GASTRIC CONTENTS WHEN SALIVA IS SWALLOWED.



mens were analyzed for free and total acidity, by the method stated above, and for amylase activity by the method of starch hydrolysis and sugar determination. The total volume of the saliva and its amylase activity also were determined. This experiment was performed 5 times on 3 patients. Later the above experiment was repeated with these same and other patients lying on the abdomen with the head low. A mouth gag was inserted to prevent swallowing? These precautions precluded any chance of the saliva being swallowed or draining into the esophagus. Seven experiments with these modifications were carried out on 4 subjects.

It is apparent from the Table I and Figs. 1 and 2 that when the patient lies on his side there is a decrease in free acidity which promptly follows the injection of mecholyl. The free acidity completely disappeared in 4 out of 5 experiments and the secretion also changes from serous in character to a ropy, mucinous fluid. The actual volume changes of the aspirated gastric secretion are necessarily inaccurate because of frequent duodenal regurgitation and occasional incomplete evacuation due to mucosal plugging of the Levine tube. When the patient is placed on his abdomen, however, and precautions taken against swallowing saliva there is an equally prompt rise in free acidity with a flow of serous gastric juice following a similar injection.

Gray and Ivy (8) had reported a reversal effect on the gastric secretion in gastric pouch dogs. These dogs had both vagi cut and were given continuous injections of histamine until the gastric secretion was constant in volume and acidity. Then the subcutaneous injection of 0.1 mgm. of mecholyl caused an increase in gastric secretion while 1 mgm. similarly injected caused a decrease in acidity. These investigators felt that this reversal explained the alkaline gastric secretions following large injections of mecholyl observed by Myerson and Ferguson and Smith.

We feel that it is evident from our experiments that 25 mgm. of mecholyl injected subcutaneously in human subjects has caused neither a marked decrease in degree of free hydrochloric acid nor a marked change in character or volume of the gastric secretion when care is taken to prevent the swallowing of saliva. It is clear that when a marked change is recorded that it is due to swallowed saliva. This fact is established by the almost identical

degree of the amylase activity of the saliva and the gastric secretion on several occasions when they were simultaneously collected; it is further borne out by the changes in total volume of the saliva, collected after the mecholyl, in the same patients, when studied under identical conditions, except those modifications designed to prevent the swallowing of saliva.

The saliva of the human subjects was studied on several occasions. It was found to change in its reaction to litmus paper from slightly acid on fasting to alkaline following mecholyl injection. On titration with .02 N sodium hydroxide the total acidity was observed to change from 12 to 4 in some instances and there was in each case a decrease in total acidity. The great increase in thick, ropy mucin probably acts as both a diluent and buffer. The value of this buffer mechanism was demonstrated by mixing in vitro various amounts of gastric secretion of known free and total acid concentration with the alkaline saliva. In these mixtures there was a greater decrease in free acidity than the dilution factor, while the total acidity decreased more nearly in proportion to the dilution. This greater decrease in free acidity is a crude indication of the buffer value of the saliva. The great viscosity, tenacity and incomplete miscibility of the saliva may account for the variation from the predicted decrease in total acidity.

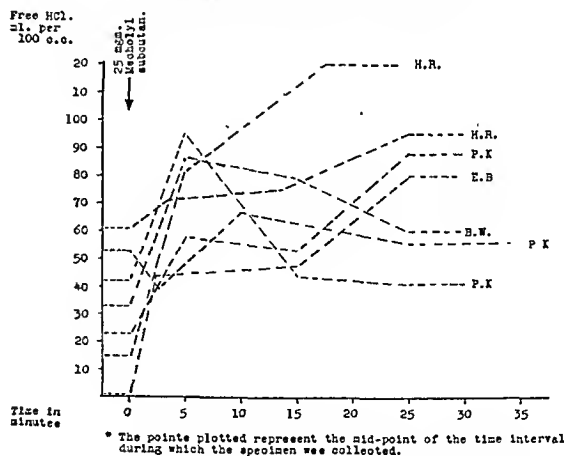
It appears from our studies that while mecholyl injected in this dosage usually caused a slight to marked increase in gastric acidity, unless great care was exercised enough alkaline, mucinous saliva was swallowed to buffer the gastric secretions. It, therefore, seems that if all the saliva is purposely swallowed an efficient buffer may be available for use in cases of gastric hyperacidity. The clinical application of this principle is being investigated.

CONCLUSIONS

1. There was no outpouring of mucinous, alkaline gastric secretion in 6 rabbits after subcutaneous injections of 2 and 4 mgm. of mecholyl chloride.
2. There is no marked change in the free and total

FIG. 2*

EFFECT OF MECHOLYL ON FREE ACIDITY OF GASTRIC JUICE IN HUMAN SUBJECTS WHEN SALIVA IS NOT SWALLOWED.



acid of the gastric contents in rabbits after these dosages but because of large amounts of solid gastric residue these figures are not wholly accurate.

3. In 3 cats no free hydrochloric acid was present in the fasting gastric specimen nor did any appear after subcutaneous injections of 2, 4 and 10 mgm. of mecholyl chloride.

4. When proper care is taken to prevent the

swallowing of saliva there is no marked change in character in the gastric secretions in human subjects following the subcutaneous injection of 25 mgm. of mecholyl chloride.

5. There is in most instances a slight to marked rise in free and total acidity following such an injection.

6. There is a marked increase in flow of saliva which becomes mucinous and more alkaline.

7. The accidental swallowing of less than one-half of the saliva more than neutralizes the rise in gastric acidity and the purposeful swallowing of the entire

amount is suggested as a possible therapeutic measure in cases of hyperacidity.

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History and Development of Gastric Analysis Procedure*†‡

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I. INTRODUCTION

GASTRIC analysis is used today almost universally as an aid in diagnosis. Nevertheless, there is an exceedingly widespread dissatisfaction with it, amounting with many individuals and institutions to a forthright negation of all but a modicum of diagnostic significance. Why is this so, and what does it portend for the future of gastric analysis? And what, if anything, can be done about it? As workers in a research laboratory devoted entirely to gastro-intestinal physiology and its clinical applications, we realized that this is one of the foremost problems which we face today. The matter is vital because every effort at studying gastric physiology in the human—both normal and pathological—must ultimately be based on the procedures of clinical gastric analysis.

Hence, we started last year a series of investigations in an effort to work out a procedure which may prove more satisfactory to clinicians and research workers alike. For this purpose it was essential to have sharply defined in our minds the present trends in gastric analysis procedure. The latter, in turn, necessitated a thorough historical survey of the problem in all its phases, in order that we might attain some historical perspective on our subject. A search of the gastro-enterological literature of the last 60 years yielded enough material for a monograph rather than a short paper on the subject. Hence the present report will be devoted chiefly to the criticisms which have been leveled against present procedures and to the developmental trends which are already discernible in response to these criticisms.

Taking an airplane view of the entire span of gastric analysis procedure, we perceive four well-defined periods of development. These periods may be characterized as follows:

1. The primitive, non-diagnostic period (up to 1883)
2. The single specimen, diagnostic period (1883-1914)
3. The fractional analysis period (1914 to date)
 1. A period of physiological analysis.

These subdivisions are clearly differentiated by the development of a new technique in each case, yet it must be noted that chronologically they overlap to a considerable degree. Thus the primitive period gave way to the early diagnostic period with the introduction of a well-defined test-meal and the rubber stomach tube; fractional analysis, in turn, was made possible by the development of the fine, soft rubber catheter; the modern trend away from a search for simple clear-cut diagnostic procedures and toward an analytically physiological view of the patient is characterized by a statistical outlook. The extent to which the individual periods overlap in time will become apparent as we proceed.

II. THE PRIMITIVE, NON-DIAGNOSTIC PERIOD (UP TO 1883)

Interest in the secretory products of the gastric mucosa was but sporadic until relatively recent times. Robertson (113) quotes Van Helmont (1648) as writing of an acid ferment responsible for digestion. In 1692 Viridet obtained gastric juice for gross study by killing animals for this specific purpose. Sixty years later (1752) Reaumur studied the gastric juice of birds by inserting a sponge into the stomach and expressing the juice after its withdrawal. Human gastric juice was first studied carefully by Reuss (1760) in instances where it could be obtained from individuals capable of vomiting on request.

These studies belong to the archaic period of the study of gastric secretion, which preceded the discovery of hydrochloric acid in the stomach by Prout in 1821. Not until 1833 do we encounter the first experimental efforts on humans in the classical studies on Alexis St. Martin; and ten years later the experi-

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mental approach in gastric physiology was initiated by Bassow and Bloudot who duplicated the St. Martin gastric fistula in animals. Thereafter, forty years were to pass before human gastric juice became readily available for careful study. During this period the first lines of analysis of the problems of gastric secretion were gradually laid down on the basis of animal experimentation by Klemensiewicz and Heidenhain. It was during this period, also, that technical advances in the vulcanization of rubber—initiated by Charles Goodyear in 1844—first made possible the clinical use of the stomach tube.

The stomach tube owed its introduction into medical procedure to its therapeutic possibilities rather than its applicability to diagnostic medicine. According to Garrison (48) the principle and practical application of the stomach tube, or stomach pump, probably evolved before 200 B.C. Its utility in withdrawing ingested poisons was recognized by Monroe Secundus in 1767, and John Hunter (1790) utilized it to feed a patient with an esophageal obstruction. In this country it was first used by Physick, who employed it for purposes of lavage in cases of poisoning.

A further and important extension of its use is due to Kussmaul (1869) (74) who aspirated the stomachs of patients with pyloric obstruction due to duodenal ulcer, thus affording symptomatic relief and prolonging the lives of many of them. Despite the frequency with which he obtained gastric juice by means of these aspirations, his interests were so obviously therapeutic that he apparently never examined the contents chemically and he recorded only the morphological elements and the gross physical characteristics of the fluid. However, as a result of the work of so famous a clinician from an internationally known clinic, the therapeutic application of the stomach tube soon became very popular.

III. THE SINGLE-SPECIMEN, DIAGNOSTIC PERIOD (1883-1914)

It was only four years later, in 1883, that the possibilities inherent in the stomach tube for diagnostic purposes were first reported. In this year von Leube (77) aspirated stomachs after ingestion of a standardized meal—primarily for the purpose of determining the amount of residue but also to determine the concentration of acid and pepsin. His interests were chiefly those of a physician interested in gastric diagnostics, and as such he devoted his attention to the degree of digestion of the test-meal as well as to the amount which remained in the stomach after a given time interval. In this way he thought to obtain a picture of the digestive and motor capacities of the stomach in various disorders.

This elementary physiological point of view, which was lost for several decades but is now cropping up again, is based on the following reasoning: The composition of the gastric contents at a given time is dependent on a large number of interrelated variables. It is obvious that the most important extra-gastric factors which determine this composition are the stimulus (i.e., the test-meal) and the time interval between its application and removal of the specimen. With these factors kept constant, the only uncontrolled variables presumably were those inherent in the status of the gastric mucosa, and thus the result of the test would reflect the pathological changes in these variables and so yield information of diagnostic value.

For a standard gastric stimulus, von Leube used a mixed meal consisting of beef bouillon, a beef steak, pureed potatoes and one slice of white bread. This was ingested in place of the usual noon meal, and after a seven hours' fast the gastric residue was aspirated and examined for food residues as well as for the presence of acid and pepsin. In this fashion he was able to evaluate the motor function of the stomach as well as its capacity to secrete in response to a standard test-meal.

Despite von Leube's interest in the secretory phenomena, his main objective was to establish the emptying capacity of the stomach—in which he undoubtedly succeeded from the practical point of view. For the purpose of testing gastric motility, von Leube's test meal was very satisfactory. He performed only a single aspiration; probably that was all that could be tolerated by his patients because of the large, stiff tube which he used. In spite of this, the technique became extremely popular on the continent, due in no small measure to the efforts of Ewald, Boas and Riegel at further standardization and simplification of the test-meal. Beyond such changes in the nature of the stimulus, and the reduction in time interval from 7 hours to 1 or one-half hour, these latter investigators contributed very little to the procedure introduced by von Leube—although their studies were numerous and well conducted. Concerning the nature of these test-meals more will be said later.

As early as 1891, however, the need, for clinical purposes, of a more dynamic picture of the course of the secretory, digestive and motor characteristics of the stomach began to be realized. In that year Hayem and Winter (56), using the Ewald-Boas test-meal and the tube in vogue at that time, aspirated gastric contents of fasting patients; aspirations were performed at 30 minute intervals after the administration of the test-meal until the stomach was empty. They plotted curves of free, total, and combined acidity and thus succeeded in combining the chemical and motor test-meals in a single examination. In 1895 Schüle (121) performed a similar study in which he reduced the interval between aspirations to 15 minutes. These were the sole studies of their kind until the twentieth century when advances in rubber technology made it possible to create a tube which could be more readily used for this purpose.

IV. FRACTIONAL ANALYSIS PERIOD (1914 TO DATE)

The need for a simple method of following the course of gastric secretion and digestion could be met only by the development of more flexible tubes of smaller caliber, than those employed by von Leube, Ewald, etc. Although Gross (55) used such a tube in 1893, it was not until 1912 that its systematic use became general. In that year Ehrenreich (35) using such a flexible, narrow rubber tube with the Ewald-Boas test-meal, followed the example of Winter and Hayem and of Schüle and withdrew small specimens for analysis at 10 minute intervals following ingestion. The procedure did not become popular, however, until 1914 when Rehfuss (110), in this country, described his well-known tube. With this innovation, one may say that the modern period of gastric analysis was truly under way. In the years that followed, the tube was modified by numerous investigators, such modifications usually involving the shape, size and

fenestration of the tip. An extensive historical review of the various modifications may be found in a recent article by Moses Einhorn (37). In all essentials other than the composition of the test-meal the principles and procedures established by Rehfuß have remained unchanged, until this very day.

The usual tube is about 1 meter long with an outer diameter of 6-7 millimeters. Its tip is formed by a stainless metal (gold-plated) bucket. The tube is marked off at 50, 65 and 80 centimeters from the tip and it is usually introduced to the 65 centimeter mark for gastric analysis. The test-meal varies with the preference of the clinician. It is worthy of note that the modern period of fractional analysis has concerned itself mainly with secretory phenomena and only to a lesser extent with the motor activity of the stomach. One manifestation of this is the fact that the noon and evening test-meals have virtually been discarded and only a breakfast test-meal is now employed.

Apart from the nature of the test-meal stimulus, the procedures involved are always essentially the same. The tube is swallowed while the patient is in the fasting state, and special attention is given to the complete expectoration of saliva. The fasting contents are aspirated and set aside for chemical analysis, after noting its gross physical characteristics such as volume, color, odor, presence of mucus, blood, or bile. The test-meal is then administered, either by ingestion or by passage through the tube, and at regular intervals thereafter specimens are removed for chemical analysis. This may be done in either of two ways:

(1) The procedure employed by Rehfuß, which is to withdraw only 10-15 cc. each time.

(2) A modification introduced subsequently, whereby the entire contents of the stomach is removed each time, mixed thoroughly, and all but 10-15 cc. returned through the tube. In either case the procedure is continued until the stomach is empty. In aspirating, only the gentlest of suction is applied, with the aid of a glass syringe, in order to avoid trauma.

The failure of the single specimen type of gastric test-meal to yield accurate diagnostic information was felt even by the earliest workers. Even Hayem and Winter, and Schüle felt that although the composition of the gastric juice obtained one hour after the ingestion of a test-meal had considerable practical significance, the results were frequently indecisive and difficult of interpretation. Also, the problem of gastric activity presented a two-fold aspect: a secretory and a simultaneous motor. It was in order to study the variations in intensity of these two functions throughout the course of digestion that they conceived the idea of the fractional test meal.

The concept basic to these newer efforts, never explicitly formulated by these early workers, was that whereas variations from normal gastric function might not be readily discovered by means of the single specimen technique, the fractional method was capable of demonstrating pathological variations in the ability of the diseased gastric mucosa to respond to a standard stimulus. It was hoped that such variations in the response of the gastric mucosa to a standard stimulus would prove to be representative of its working capacity, and hence would permit a classification of gastric secretory behavior. Amplification of this idea culminated in the formulation of the several categories of secretory activity, characterized by the degree of acidity and of pepsin activity attained by

the several fractions removed in the course of a single analysis. These categories possess the now universal designations of hyperchlorhydria, isochlorhydria, hypochlorhydria, achlorhydria, and achylia. Another classification, designated hyper-, hypo-, and apepsia is now obsolete. Emptying time, when it was considered at all, was characterized as hyper- or hypomotile by the time required for the test-meal to disappear from the stomach. With the creation of such divisions, based on the quantitative measurements of time and acidity, efforts were made to correlate the various gastric disorders with these classifications. In this way it was hoped that the procedure of fractional analysis would yield information concerning the physiological components of gastric pathology, just as radiographic and gastroscopic examinations demonstrate the anatomical components.

With the introduction of the small caliber tube into clinical work by Rehfuß, there ensued a wave of enthusiasm for the diagnostic value of the procedure. The ease with which the analysis could be performed was especially potent as a factor in its universal adoption. Shortly after its initial acclaim, however, various criticisms began to be leveled at the procedure from different directions. The bases of these criticisms may be summarized as follows:

(1) The stimulating action of the tube itself on the gastric mucosa, merely by mechanical action.

(2) Dilution and neutralization of the gastric juice by saliva.

(3) The psychic effect of the presence of the tube in the mouth and throat.

(4) Dilution of gastric juice by the test-meal.

(5) Variations in composition of the gastric contents at different levels in the stomach.

(6) Irregular duodenal regurgitation, resulting in dilution and neutralization of the stomach contents.

(7) Variation in secretory response ascribable to differences in composition of the test-meal stimulus.

(8) Wide day-by-day variations in the type of curve obtainable with any one "normal" individual; and the occurrence of "normal" curves in cases of obvious gastric disease, and of "abnormal" curves in healthy individuals.

With the exception of the last, all of these criticisms were met by Rehfuß and his associates by the following argument. It is the presumption of these criticisms that the aim of a fractional analysis is to give a picture of the secretory activity of the stomach. This is not so. To quote Rehfuß himself (110), it is to study the entire work of the stomach and, by correlating its manifestations with gastric pathology, to set up a diagnostic test in terms of this work. By the work of the stomach he meant the result of all the numerous processes which operate in "the reduction of a heterogeneous mixture of foodstuffs into a homogeneous chyme." The summation of all these processes, he contended, is adequately indicated by the acidity curve, the degree of chymification, the emptying time, and the visual evidences of pathology obtained by gross and microscopic inspection.

The last criticism, however, the basis of which may be summarized by the expression "normal biological variation," could not be coped with by Rehfuß. How can we hope to classify disease on the basis of a particular test when the responses of normal and diseased stomachs to that test are not constant and quanti-

tatively distinct from each other—in short, when there is no correlation between pathology, roentgenographic observations, and the chemical results of the fractional analysis. For this reason more than any other, the hope of clinicians that fractional analysis would afford a simple diagnostic procedure was doomed to failure.

In spite of their cognizance of this failure, many gastro-enterologists have continued to use the fractional technique. This may be due in part to lingering hopes, and in part to the feeling that the Rehffuss method remains a valuable aid to diagnosis. The numerous and continued efforts at refinement of the fractional technique which are apparent in the literature, however, betoken something far more important; namely, that the procedure is gradually being transformed into an instrument of precise physiological research concerning the individual component elements of gastric behavior. The modern clinician is becoming aware that there is no short road to diagnosis and that he can understand his patient only by comprehending the latter's individual physiological responses. This, we believe, is the beginning of a new scientific period in clinical gastric analysis. Before discussing it, however, we must first describe the historical development of test-meals and of the chemical-analytical methods which are employed today.

V. TEST-MEALS

Of all the many test-meals which have been and still are employed for gastric analysis, the "test breakfast" proposed by Ewald and Boas (41) in 1886 takes precedence as a standard. Previous to this (1883), we find the following mixed meals which were proposed for the study of emptying time or of digestive activity, in contradistinction to secretory activity *per se*. The "dinner meal" of von Leube (77) consisted of soup, beef steak and white bread, and was aspirated after seven hours. A similar mixed meal consisting of veal, white bread, and other foodstuffs was employed by Ewald and Boas (40) in their early work (1885), but it was soon discarded for the similar "test breakfast" as we now know it. About the same time, Riegel (112) used a mixed meal of 400 cc. of soup, 200 gm. of beef-steak, 50 gm. of white bread, and 200 cc. of water; this also was aspirated for examination seven hours after ingestion. The mixed "evening test-meal," proposed by Boas in 1894 (14) was also intended to be chiefly a test of motor sufficiency; but because of its inadequacy it was subsequently improved by the addition of a tablespoonful of currants (Strauss (130)), six prunes (Bourget (19)), or 1-2 grams of bismuth subcarbonate (Robin (114); Grandauer (54)).

The Ewald meal as it is used by various workers today—which differs from these others in being designed for secretory as well as motor studies—varies widely in its composition. It may consist of any one of the following solid foods, accompanied by a fluid; bread, white bread, toast, rolls, sweetened or unsweetened crackers of various kinds—all either buttered or unbuttered and in quantities which vary from 30 to 70 grams. The fluid portion of the meal may be either water or tea (without sugar and cream), in volumes which vary from 200 to 500 cc. According to Lyon (84), however, Ewald himself used 50 grams of bread or roll and 350 cc. of water, but in their original paper Ewald and Boas used 35 grams of white bread with two glasses of tea or 400 cc. of water. Numerous

modifications of this meal have been introduced because it is non-palatable and does not develop psychic secretion, e.g., arrow-root cookies as used at the Mayo Clinic (Eusterman and Balfour (39)) and shredded wheat biscuits or soda crackers as recommended by Crohn (26) for office use.

From the very beginning these dietary test-meals found disfavor among clinical workers because of their complexity, and especially because of their content of solid substances. Also, reliable determinations of acidity in these mixtures were well nigh impossible unless each fraction was filtered, but this also introduced an error because of the difference in titre before and after filtration (Pfaundler (104), Vos (138)). Hence, in an effort to use a dietary substance which is entirely fluid, Talma (133) in 1895 administered through the stomach tube 3 per cent Liebig's extract which had previously been neutralized with NaOH. Since then this meat extract preparation has been employed in various concentrations and volumes by numerous investigators (Mintz (95), Skaller (127), Lewin (80), Martini and Beck (87) and Wilhelmj (139)). Similarly, the original oatmeal test-meal of Boas was made popular in this country by Crohn and Reiss (27) in 1917; four years later Ryle (116) introduced it into England. In 1910, Fuld (44) proposed a solution of caramel, 1 tablespoonful in 200 cc. of water; and in 1928, Orlawsky (100) used a drink containing cabbage juice—but neither of these has found very wide application. In a desire to use a pure chemical substance which is also, to some extent, dietary in nature, Kast (67) proposed the use of alcohol in a concentration less than ten per cent, since at this dilution acid but no mucus is stimulated. It was not until 1912, following its use by Ehrmann (36), that the alcohol meal became really popular and was used by such notable workers as Killing (71), Wonkhaus (145), Katsch and Kalk (68), Bloomfield and Keefer (12), and Vandomfy and Varády-Borbély (136). In spite of its very extensive use, however, the claim has been made repeatedly that alcohol is non-physiological and irritating—both of which contentions may be questioned—and hence should be abandoned. As a substitute for it, Katsch and Kalk (69) introduced the use of caffeine which they believed to act directly on the secretory glands; in this they probably followed Strauss (129) in his use of tea for its caffeine content. This substance has also been used by Schwab (123), among others, but as yet it has not become popular. It must be noted that, for any one of these various test-meals, the volumes and concentrations employed by the several workers who used them show considerable differences.

In contradistinction to the dietary motor test-meals previously described, the fluid test-meals were introduced with a view to evaluating the secretory response of the patient. Hence, the question naturally arises: How do these several fluid test-meals compare with each other in respect to their stimulatory activity? This problem has been carefully investigated in several laboratories, using the fractional technique, and the results indicate that 5 per cent alcohol, bouillon, tea and caffeine all give essentially the same results (Dinkin (32), Garbat (47)). What lack of agreement was observed may well be attributed to the normal daily variation of the patient or to the variations involved in the removal of individual specimens during any one analysis. Furthermore, comparison of these test-meals

with plain water, cold or warm, tap or distilled—a test-meal first proposed by Bergeim, Rehfuß and Hawk (10) and used by Moffatt, Mitchell and Powell (96) without any stimulatory results—suggested that the special test substance in each case was contributing nothing to the stimulatory action of the water itself. Hence, in spite of Crohn's preference for a food substance because of its slight gustatory attractiveness (26), it would seem that the plain water serves all the functions of these other test-meals; and since it is mechanically and chemically simplest of all, it would appear to be the one logical substitute for the purposes of gastric analysis. This conclusion may be objected to on the ground that plain water serves only as a mechanical stimulus to secretion and not as a chemical stimulus (Lim, Ivy and McCarthy (82)). But if the special chemical stimuli present in these various test-meals are contributing little or nothing to the secretory process, as appears likely from the observations reported, then why use them at all? This question cannot be answered now, but it is certainly one which merits experimental consideration.

From time to time fluid test-meals have been objected to because their emptying time, in general, is considerably less than those reported with the Ewald meal; sometimes it is even less than 45 minutes (Garbat (47)). Also, it is claimed by many workers that duodenal regurgitation is much greater with a fluid meal than with a solid one, but this difference may be entirely illusory because of the presence of the bread much in the latter. (Dinkin (32), Garbat (47), Gaither (45)). On the other hand, they point out a number of distinct advantages possessed by fluid meals: (1) They are homogenous and contain no sediment which might interfere with studying the cellular elements or in titrating. (2) They are free

from alkaline salts which might reduce the total acidity values, and some of them have no effect on the free acidity either. (3) They can be removed more easily through a small duodenal tube than a bread-containing mixture. (4) Above all, they permit of a degree of standardization and of purity such as cannot possibly be attained with a food test-meal.

Unfortunately none of the fluid meals give any reliable indication of the emptying time in those cases which show retention for one hour or more. In the case of the Ewald or other food-containing test-meals, the amount of meal retained after, say, one hour was usually taken as an index of emptying time. With the use of fluid test-meals this criterion is frequently impossible; to offset the difficulty, it has been proposed from time to time that a small amount of some colored substance be incorporated before administration, in much the same way that raisins and currants were added to solid meals. To this end Ehrmann (36) used a few drops of methylene blue, Boas employed chlorophyll, Skaller (127) introduced phenolphthalein (which becomes colored on alkalization) and Lewin (79) a few drops of phenol red. Absence of indicator substance noted by qualitative examination of successive specimens indicated the time at which the last traces of test-meal had left the stomach, i.e., the emptying time.

In view of the possibility that minute amounts of the indicator may adhere to the gastric wall for some time after the bulk of the test-meal passes through the pylorus, we believe that such a qualitative technique is unsatisfactory. Instead, the situation calls for a quantitative evaluation of the test-meal residue in each fraction—a procedure which we will discuss more fully below.

(To Be Continued)

Peptic Ulcer---The Effect of High Protein Diet on the Behavior of the Disease*

By

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ON a theoretical basis a high protein diet should favorably influence the symptom-complex of peptic ulcer. Proteins can neutralize acids by their acid-binding properties. Peptic activity can be inhibited by the acid-combining properties of proteins or by the "competitive retardation" of the products of peptic digestion of proteins. Again, proteins supply ample amino acids and would restore a deficiency believed by many to be a causative factor in the production of peptic ulcer.

High protein diets have been advocated in the past by Lenhartz, Wagner, Kaufman and others (1). With the advent of the Sippy regime of milk and cream, frequent feedings and alkalies, the protein diet lost its popularity.

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S. J. submitted September 29, 1935.

Recent animal experiments seem to indicate that proteins play an important role in the production and prevention of experimental ulcers. Hoelzel and Da Costa (2) and Weech and Paige (3) have shown that a deficiency of protein in animal diets results in gastric ulcer formation. In our own experimental investigations (4) we have shown that supplementary protein feedings in animals prevented experimental "pepsin-hydrochloric acid" gastric ulcers.

CLINICAL STUDY

On the basis of the above considerations we began the administration of a high protein diet to patients with peptic ulcer and studied the effect upon the behavior of the disease.

A group of forty patients with a clinical history and roentgen-ray corroboration of peptic ulcer was

selected from our gastro-intestinal clinic. The average duration of symptoms with remissions, was eight years and varied from one to thirty-one years. Three of the group received no previous treatment, whereas the others had been on an alkali-diet regimen on more than one occasion. The patients were given a bland, high caloric, and high protein diet consisting of approximately 150 grams of protein, 100 grams of fat and 200 grams of carbohydrate. The proteins were given in the form of lean boiled meat, chicken, cottage cheese, milk and unflavored gelatin U. S. P.*

Gelatin was selected as the added protein because of its availability, relatively low cost, non-toxicity, and the ease with which it lends itself to frequent administration. The gelatin was supplied in blank envelopes, each containing eight grams, and was to be taken hourly, between feedings, in one-quarter glass of water for seven doses daily. The amount of eight grams was given, more for convenience, since it is the regular commercial size, than for any other arbitrary reason. Most patients tolerated the gelatin well, while some disliked the taste but made no other complaints.

All patients were ambulatory throughout the study and were seen weekly at the clinic for follow-up care. These patients were observed for a period of one year and throughout this study no medication, except occasional cathartics, was given.

The patients were questioned at each clinic visit in regard to change of symptoms, particularly relief from pain. The results have been classified in three groups. The first consisted of twenty-eight patients who had immediate relief of all symptoms. Most of this group stated that under this regimen they felt much better than with the alkali-diet treatment which they had had during previous relapses. The second group consisted of eight patients who had "fair" results. In this group the high protein diet with frequent feedings gave them no better nor worse results than the alkali-diet regimen. The third group of four patients had no improvement. The records of these patients show that at no time had their symptoms been controlled either by alkalis or foreign protein injections. The continued use of the high protein diet by the patients who were improved was stressed and but few recurrences were noted throughout the year.

X-ray studies on these patients showed a disappearance of the original niche in many instances. In others we observed slight or no change in deformities. In accord with other investigators we found that the objective findings on the roentgenograms did not always parallel the symptomatic relief.

Gastric analyses on some of these patients, using the double histamine test and gelatin, showed that there was a long period of binding of both free hydrochloric acid and pepsin. Work along these lines is being continued and will be published in a subsequent paper.

Table I shows the immediate results in patients on a high protein diet when compared with results of diet-alkali treatment.

DISCUSSION

It has often been stated, that patients with peptic ulcer can be fed almost anything, and a certain number will respond favorably. Spontaneous alleviation of symptoms in peptic ulcer patients extending over a long period has been reported by Emery and

Monroe (5) in as many as forty per cent. It is, however, striking that in our group of forty patients about ninety per cent were symptomatically improved and remained so for a long period. This is higher than their group of spontaneous remissions. The mechanism of this favorable effect is not clear. Several possibilities suggest themselves. It is possible that in our group, because of the high caloric diet, the patients gained weight and overcame any tendency to under-

TABLE I

	With High Protein Diet		With Diet-Alkali Treatment	
	Number	Per Cent	Number	Per Cent
Number of patients	40		37	
Symptom free	28	70.0	13	35.13
Moderate improvement	8	20.0	11	29.73
Unimproved	4	10.0	13	35.13
Total improved	36	90.0	24	64.9

nutrition. A high protein diet may increase the formation of bile salts (6) which in turn may relieve symptoms in certain patients (7). The frequent feedings of protein which in this study was gelatin, apparently caused more prolonged neutralization of the gastric juice. It is also possible, as pointed out by Pottenger (8) that gelatin, by its hydrophilic colloid action, lessened gastric irritation by absorbing the digestive secretion of the stomach. Gelatin is a good source of glycine, which, as shown by Brand, et al (9), is a good muscle and tissue builder, and may favorably influence the healing of a peptic lesion.

SUMMARY AND CONCLUSION

1. Based on results in the production and the prevention of experimental gastric ulcer in animals, a high protein diet was used in the treatment of forty patients with peptic ulcer.

2. The high protein regimen consisted of a mixed diet with hourly feeding of gelatin between meals.

3. Symptomatic relief was noted in ninety per cent of patients studied.

4. The theoretical considerations for the use of high protein diets are presented.

5. We feel that this method, though not considered as a specific, has a definite place in the management of peptic ulcer, especially so in cases that do not respond to drug therapy.

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*The gelatin was supplied by the courtesy of the Knox Gelatin Co. of New York.

The Value of Gastroscopy in the Diagnosis of Phytobezoar: Case Report

By

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and

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PHYTOBEZOAR (food-ball), while not common, occurs frequently enough to justify its consideration in the differential diagnosis of obscure gastrointestinal conditions. There is no characteristic symptomatology. It may simulate ulcer, gall bladder disease, or gastric carcinoma. In general, epigastric

pain can be carried out with relatively little discomfort or danger to the patient. The first case of phytobezoar to be visualized through the gastroscope was described in 1936 by Moersch and Walter (8). The case reported in this article is, so far as can be determined, the second to be diagnosed by gastroscope.

CASE REPORT

W. T. H. (History No. 97618). A 52 year old white travelling salesman entered Duke Hospital on February 18, 1938, giving a history of epigastric distress over a period of two years. The onset of his illness was gradual. He first complained of gas and fullness in the upper abdomen with a dull aching pain in the epigastrium, coming on at any time and not related to meals or re-



Fig. 1. X-ray showing an indefinite irregularity along the lesser curvature.

pain is an outstanding feature, and hemorrhage may occur (1).

A characteristic filling defect is frequently seen by X-ray (2, 3, 1, 5, 6, 7), and the correct diagnosis is usually made before operation. However, if the mass is small and the patient a large, heavy-set individual with a stomach high up under the diaphragm, the diagnosis by X-ray is rendered more difficult and sometimes impossible.

Direct inspection of the interior of the stomach is obviously of the greatest value in such cases, and by

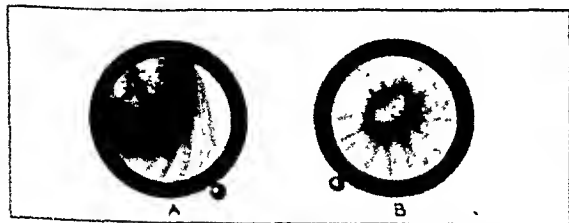


Fig. 2. Artist's drawing of the mass as seen through the gastroscope. A—Mass apparently attached to the wall of the stomach. B—Mass in the pyloric canal.

means of the Wolf-Schindler flexible gastroscope this

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Submitted May 21, 1938.



Fig. 3. X-ray showing filling defect near the pylorus.

lied by food. He soon began vomiting with each attack, which afforded immediate relief, but the attacks increased in severity. On one occasion, one week before admission, he vomited a small amount of dark blood and later had a tarry stool. He had lost about forty pounds since the onset of his illness.

The routine examination was entirely negative except for a moderate enlargement of his heart and hypertension, his blood pressure being 190/120. The abdomen itself showed nothing of interest.

There was a slight secondary anemia; the hemoglobin

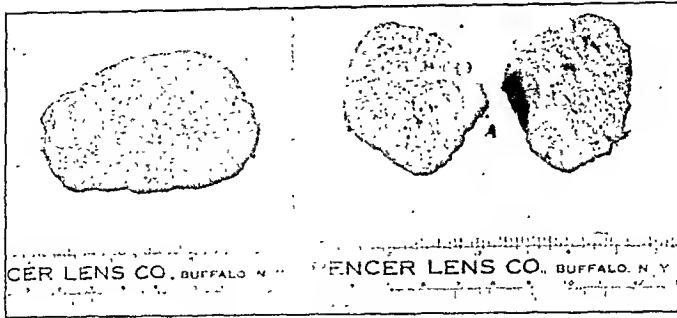


Fig. 4. Photograph of specimen.

was 72% (11.2 grams), and the red count 4,200,000. The Wassermann reaction was negative. Stool examination showed a 4-plus Benzidine. Urinalysis was negative. A tentative diagnosis of carcinoma of the stomach was made.

Gastro-intestinal X-ray examination, on February 24, showed a 30% gastric residue and an indefinite irregularity along the lesser curvature (Fig. 1). There was no filling defect. Gastric analysis revealed 60 degrees of free HCl. The stomach contained a large amount of gas.

Gastroscopy: On February 25, a Wolf-Schindler flexible gastroscope was passed and the interior of the stomach examined. A large black mass (Fig. 2A) was seen which was smooth and glistening and apparently 3 to 5 cm. in diameter. It seemed to be attached to the posterior wall and did not move on rotating the patient. Gastroscopy was repeated 5 days later, and the mass was observed in the pyloric canal (Fig. 2B).

On March 3, the gastro-intestinal X-ray series was repeated. There was no evidence of ulcer though a filling defect, not seen in the first examination, was observed near the pylorus (Fig. 3).

Operation: On March 7, under spinal anaesthesia, Dr. George Joyner removed the foreign body with ease. The patient had an uneventful convalescence and has been entirely symptom-free since the operation.

Pathological Report (Dr. Phillip Parsons). Gross appearance: The specimen (Fig. 4) measured roughly 9x4x3 cm. It was very black on the surface, but the inside was a light brown and granular. Microscopic section: Vegetable matter with many fat cells.

Chemical analysis (Dr. Haywood Taylor). This material gives no test with the usual protein reagents. There is a small amount of fatty material, and it is partially soluble in the usual cellulose solvents. It gives a good test

for lignin, and apparently the material is of a woody substance.

DISCUSSION

The development of a food-ball in the stomach is frequently associated with the ingestion of persimmons. This patient stated that he eats at least a quart of persimmons every fall, and has done so for the past thirty to forty years.

While the diagnosis can usually be made by X-ray, still there are cases in which no filling defect can be detected even after a most careful examination. In such cases, the diagnosis could be made readily by gastroscopy.

SUMMARY

A case of phytobezoar, in which the diagnosis was made by gastroscopy and confirmed by operation, is reported. The importance of gastroscopy as a diagnostic procedure in obscure gastro-intestinal conditions is emphasized.

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Ulcerative Colitis of 28 Years' Duration With Recovery

By

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THE purpose of this paper is to present a case of ulcerative colitis which was etiologically undiagnosed for 28 years. Because of the long duration of the illness, the nature of the infection, its many interesting manifestations and the complete recovery, the case is worthy of record.

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The author is indebted to Dr. Milton G. Wasch for the complete review of the X-ray films.
Submitted April 27, 1936.

REPORT OF CASE

History: On May 12, 1930, M. F., white male, age 50 years, was admitted to the gastro-intestinal clinic of the Jewish Hospital of Brooklyn, complaining of a bloody diarrhea of 23 years' duration. He gave the following history:

In January, 1907, a few weeks after his marriage at the age of 27, he was stricken with a bloody diarrhea associated with severe pains in the lower abdomen and sacral region. He was admitted to a hospital where his blood,



Fig. 1. 1931. Opaque enema study. Spastic cecum, transverse and descending arms. Complete loss of normal haustration. Coarse irregular peristalsis, finer movements of colon lost. Incompetent ileocecal valve with considerable of the clysmia in the ileal coils.

urine and stools were examined but nothing of significance was found. After eight days he was discharged with less abdominal pain though the diarrhea continued. Private physicians were consulted who repeated stool examinations, but no causative agent was discovered. X-ray studies showed the disease to be a colitis. Countless medicaments were prescribed but without benefit. The patient learned by experience that castor oil controlled the bowel discharges for as long as one week. In later years however, even this remedy did not control the diarrhea. The rectal discharges were often so spontaneous that the distance from the adjoining room to the bathroom required too much time to cover without soiling his clothes. The use of specially tailored water-proof trousers enabled him to keep his business appointments. Five years after the onset of the illness, at the age of 32, the patient developed a generalized eczema over the entire body, a bilateral eczematous blepharitis, and sycosis barbae of the chin. This skin condition continued for 23 years and only disappeared for short periods of time about every two or three years in spite of all types of medication. In 1914 a hemorrhoidectomy was performed at Bellevue Hospital. The operative site apparently healed well and the patient thought that he had less blood in the stools following the operation. In the winter of 1929 he lost all his hair due to a vesicular and pustular eruption of the scalp. Towards the end of the winter as the lesions healed his hair grew back. On the advice of physicians he had all his teeth extracted in order to remove all possible foci of infection.

The remaining history was of no importance. The patient was always well and could not account for the source of the infection. He was married. His wife was living and well. She gave birth to six children during her husband's chronic ailment and all are well. No one in the family ever suffered with diarrhea. The family history was irrelevant.

The patient was treated at the gastro-intestinal clinic

for a period of 15 months. Diagnoses were made at various times of chronic nonspecific ulcerative colitis, achylia gastrica, pancreatic dysfunction, fermentative dyspepsia, and emotional diarrhea. Therapy for these conditions was ineffective.

First Admission: On August 19, 1931, the patient was admitted to the In-patient department for further study. His temperature, pulse and respirations were normal. He was emaciated but well oriented and cooperative. His hearing was somewhat impaired. The positive findings were mainly those of generalized eczema, chronic eczematous bilateral blepharo-conjunctivitis, sycosis barbae, hypertrophied tonsils, toothless gums, postnasal drip, emphysema of chest, marked left lower quadrant tenderness, and right inguinal hernia. A gastro-intestinal roentgen study in the clinic on March 17 and again in the In-patient department on August 22 produced similar plates (Fig. 1). The large bowel emptied in 24 hours indicative of hyper-peristalsis. There was complete loss of haustrations and a marked irregularity of its lumen indicating an advanced stage of colitis. The enema passed through an incompetent ileo-cecal valve. The entire colon from rectum to cecum took part in the pathological process. (Stool examinations were done on the same days with the barium X-rays and therefore invalidated the stool studies). The proctoscopic examination revealed an edematous, reddened, diffusely ulcerated mucous membrane not characteristic of a specific infection.

Laboratory Studies: Examination of the blood revealed a hemoglobin of 70%, red blood cells 4,130,000, white blood cells 6,800 with polymorphonuclear cells 67%, lymphocytes 28%, eosinophiles 2%, mononuclears 3%, Wassermann and Kahn tests negative; blood sugar 105 mg., urea nitrogen 9 mg., creatinine 1.6 mg. The urine analysis was normal. Repeated stool examinations were negative for ova or parasites. Gastric analysis revealed a free hydrochloric acid of 12 and a total acidity of 20. Duodenal aspiration showed an occasional white blood cell and epi-

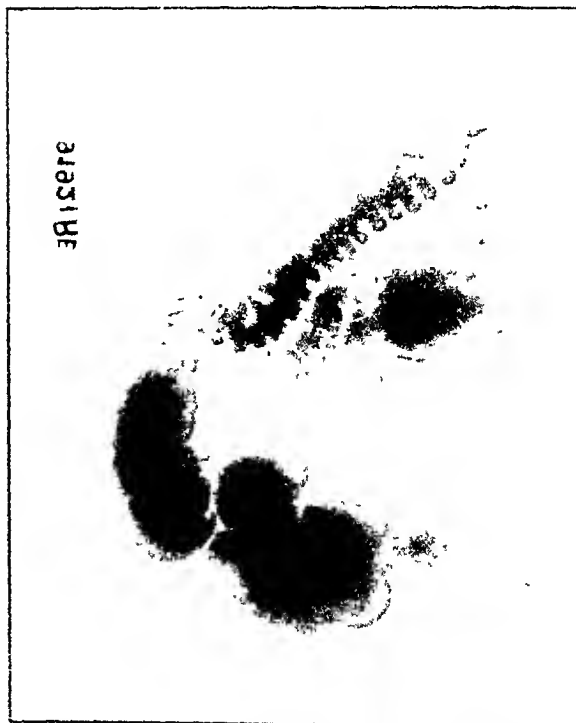


Fig. 2. 1932. Colitis apparently controlled with restitution of normal markings throughout. Note normal cecum and the well defined regular haustrations of the transverse and descending arms.

thelial cell, and was sterile on culture. There was no trypsin or amylase present. Basal metabolic rate was -6%.

The patient was discharged with the diagnosis of chronic nonspecific ulcerative colitis and referred to the

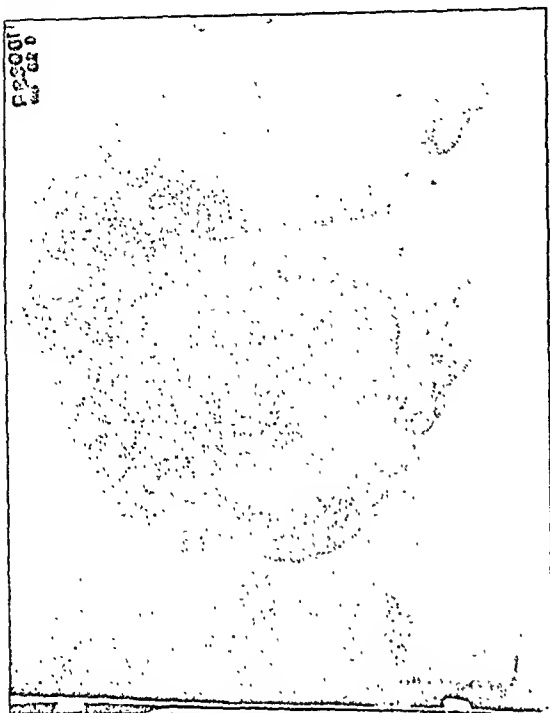


Fig. 3. 1934. Coarse peristalsis with loss of normal haustration again present (see Fig. 1) recurrence of colitis.

Out-patient department for further care. A colon study on July 19, 1932 (Fig. 2) revealed marked anatomical improvement even though the patient still complained of diarrhea. The haustrations returned and were well marked and regular. The smooth rigid tubal outline could not be seen.

The patient was treated for the generalized eczema of the body in the Dermatology clinic from the time of his admission to the Out-patient department in May, 1930. The results were discouraging with all types of internal and external medications. From May to October, 1933, he was given weekly intravenous injections of sodium iodide. Although the skin condition did not show improvement the diarrhea stopped for five months—for the first time since the onset of his illness. In view of the etiology later found the effect of the sodium iodide on the diarrhea is interesting. Iodine is an excellent amebicidal drug. Potassium iodide orally had no effect on the diarrhea.

Second Admission: It occurred to some of the clinicians that reduction of the activity of the thyroid gland might also diminish peristalsis. The patient was therefore hospitalized on June 15, 1934, and given X-ray therapy to the thyroid. Six treatments were given without the slightest benefit. On June 23, 1934, another colon study with a barium enema revealed the smooth tubal appearance of marked inflammation (Fig. 3). There were no signs of haustrations and marked narrowing and irregularity of the lumen could be seen. The picture was similar to that seen in 1931.

In July, 1934, the writer described an instrument (1)

by means of which exudate could be aspirated from the ulcers under direct vision through the sigmoidoscope. The patient was therefore called back to the clinic for further etiologic investigation by this method. On July 8, 1935, an aspirated specimen obtained from the ulcerated lesions under direct vision through the sigmoidoscope and immediately examined on a warmstage microscope revealed numerous motile amebae of the histolytica type. This solved a veritable mystery of 28 years' duration.

Third Admission: On the following day the patient was readmitted to the hospital for anti-amebic therapy. An electrocardiogram revealed myocardial damage. The cardiologist felt however that emetine hydrochloride given under close observation was not contraindicated. The drug was given intramuscularly in doses of one grain for ten days. The diarrhea stopped promptly and the patient was discharged two weeks after admission. Carbarsone, grains four, B.I.D. for ten days, then Vioform, grains four, six times daily for sixteen days were given orally in the Out-patient department with complete recovery. The patient gained 25 lbs. within nine months, and noted gradual



Fig. 4. 1938. Tubular bowel, peristaltic tone lost, lumen narrowed, haustrations missing. Atonic colon, secondary to chronic colitis. Note involvement of upper sigmoid in pathological process.

disappearance of the skin lesions. On April 30, 1936, in the clinic, sigmoidoscopic examination revealed a smooth, finely scarred granular mucosa without evidence of congestion, petechiae, or ulcerations. He was last seen at the presentation of his case to the Staff Society on January 11, 1938, feeling perfectly well. He had gained almost 70 lbs. in weight and had not suffered with the skin lesions since the specific treatment was instituted. A barium enema on this day showed a smooth, narrowed, shortened colon completely lacking haustral markings (Fig. 4).

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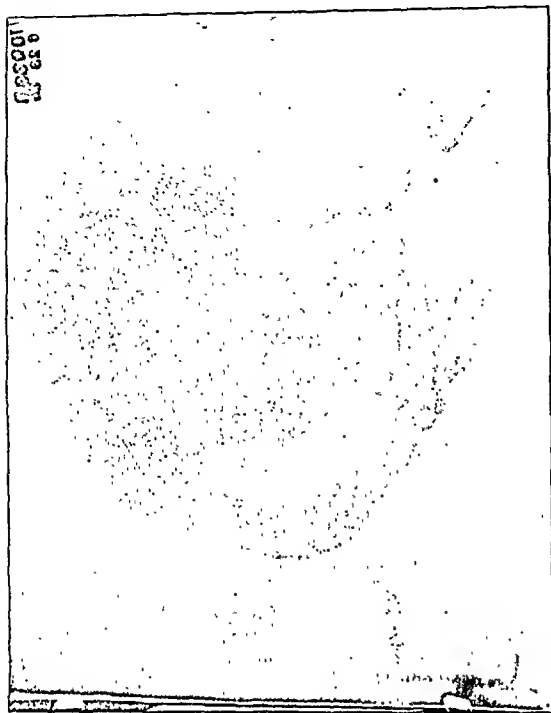


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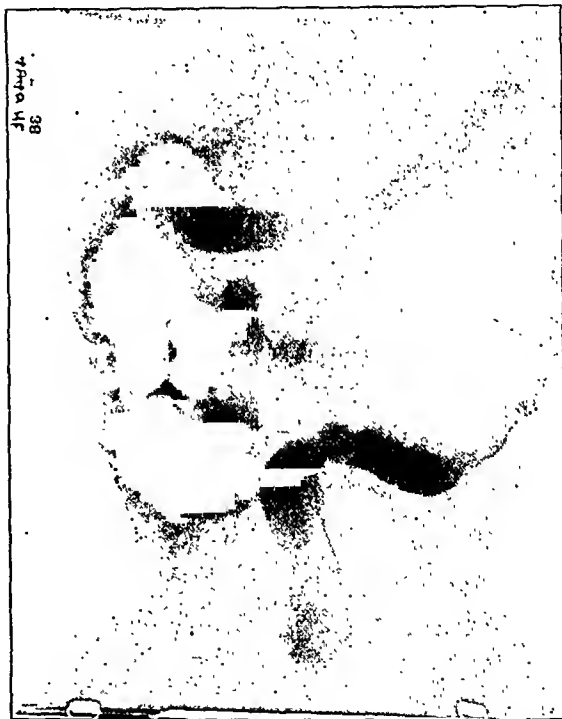


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While the patient was in the hospital an experiment was carried out which definitely and completely proved that stool examinations as done routinely in many hospitals are

frequently misleading and embarrassing to the clinician. The following table presents the facts:

Aspirated Exudate vs Stool Specimen

	Aspirated Specimen	Stool Specimen
July 8, 1935	amebae	
July 11, 1935		negative
July 12, 1935	amebae	
July 13, 1935		negative
July 22, 1935	amebae	

COMMENT AND SUMMARY

This patient suffered with ulcerative colitis for 28 years. The etiology of the disease remained undetermined until material for examination was aspirated directly from the ulcers and immediately examined on a warmstage microscope. The routine stool examinations were unreliable and misleading. The liver, al-

though a common secondary site of amebic infection, resisted pathologic amebic invasion. The generalized eczema of the skin as well as the acute dermatitis of the scalp with temporary loss of hair may be attributed to the effect of the parasite or its toxins. It is of interest to note that the intravenous administration of sodium iodide controlled the diarrhea for a period of five months. This would suggest its use in the more protracted cases of amebiasis where the parasites have migrated to the liver and other organs and where the use of emetine is contraindicated.

This case also shows that an amebic infection of the colon may for a short period of time spontaneously regress to a state of practically normal roentgenologic findings.

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Treatment of Operable Rectal Cancer in Poor Surgical Risks

By

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ONE of the main obstacles to routine successful treatment of operable rectal cancer is the inability of certain patients to withstand the most appropriate forms of rectal resection. This inability, which is largely determined by old age, or age associated with heart, lung, kidney, metabolic or other chronic disease, varies considerably in a miscellaneous group of patients. Due to this variation, patients may be conveniently separated, as to the possibilities of withstanding treatment, into four groups, good, medium, poor and bad surgical risks. This classification is based upon a careful history and detailed physical and laboratory investigations.

Patients who are good surgical risks may be subjected to the most radical and ideal form of rectal resection, i.e., the one-stage abdomino-perineal operation, from which the operable mortality is comparatively low. Two-stage abdomino-perineal resections are applicable to the majority of patients classified as medium surgical risks. Graded procedures are often preferable when dealing with advanced operable disease or badly infected tumors at or near the recto-sigmoidal junction. Patients classed as bad surgical risks are unsuitable for any form of radical treatment because of their very poor physical condition.

Treatment of poor surgical risks may be by irradiation or by one of the less radical forms of surgical removal. The form of surgery that is best suited for this group of cases is the perineal type of rectal resection. This operation, although not always the ideal one, as regards wide dissection and curative effect, can be performed and has a low operable mortality. It is capable, moreover, of producing a good percentage of clinical cures in the less advanced stages, and of providing a high degree of palliation in the advanced operable stages of disease. Radiation therapy, which consists of applying roentgen and radium rays to the primary tumor, is gradually increasing in popularity in this type of patient, because of the high percentage of good results. This latter method, un-

fortunately, is not suitable for routine employment in all poor surgical risks, largely because of inaccessible locations and advanced stages of disease. Both methods have a field of usefulness in this type of surgical risk. Selection of treatment can best be made by means of a working knowledge of the comparative advantages and limitations of both radiation therapy and perineal resections.

Radiation therapy is the method of choice when it offers equal or better possibilities to those afforded by resection. Treatment by the physical agents is greatly preferred by the average elderly patient; because, if successful it eliminates long periods of hospitalization and the dangers, worries and inconveniences of surgery. Moreover, in most instances the patients retain a normal or practically normal functioning rectum, since colostomy is necessary in only a relatively small percentage of cases. The reaction or strain from adequate irradiation of a small or medium sized tumor is less severe than the shock and complications that usually follow surgical removal. The reaction following irradiation of a small rectal cancer is practically nil. On the contrary, the reaction following large dosages of radon, which are necessary for large, advanced, border-line operable cancers, may be severe and prolonged for weeks. It is through careful selection of cases that severe reactions may be avoided and a high percentage of gratifying results may be obtained.

I. Rectal cancers most suitable for irradiation are the small, early, localized lesions. Such tumors must be sufficiently accessible to be approached with the protoscope so that their size, shape and degree of infiltration can be accurately estimated. Accessibility of the tumor and the surgeon's knowledge of the above factors are essential for adequate applications of radon. Medium or large sized cancers of grade I and grade II malignancy, in which the induration is clearly defined, may also be favorably influenced by the physical agents. The percentage of clinical cures

following treatment of large lesions will be somewhat less than in the case of small tumors. The problem in selecting treatment for patients with well-established disease is to determine whether the whole tumor mass can be favorably influenced and whether the irradiation reaction is likely to be more severe than the effects of surgical removal.

II. Rectal resections are reserved for the group of poor surgical risks with tumors that do not lend themselves well to radiation therapy. This group includes a fair percentage of patients with medium, advanced and large cancers. Inaccessible lesions and tumors that are poorly defined and badly infected are also candidates for resection. The majority of patients selected for surgery will be benefited by preoperative radiation therapy. This additional treatment may influence the prognosis favorably and make the resection less difficult.

RADIATION THERAPY

Radiation therapy of rectal cancer in our Clinic has consisted chiefly of external irradiation combined with interstitial implantations of gold-filtered radon seeds. A small number of cases included in this report have received local rectal applications in place of the gold seeds. In a few instances, when dealing with polypoid cancers, the electric snare has been employed to remove redundant areas of tissue in order to facilitate the adequate placement of radon seeds.

Treatment is commenced with daily, fractional, external dosage of roentgen rays. Six or seven portals of entry about the pelvis are employed. The total dosage delivered through each portal is kept within the tolerance of the skin so that permanent skin damage does not result. These treatments, which do not require hospitalization, seldom produce an untoward constitutional reaction. They are completed within two to four weeks according to the amount of both the daily and the total dosage administered to each portal.

Interstitial irradiation, which has been employed in the majority of our cases, consists of implanting gold-filtered radon seeds into the tumor mass ten to fourteen days after completion of external therapy. The dosage of buried radon must be sufficient to devitalize all the malignant cells, and, depending upon the size of the tumor, varies from 1000 to 5000 millicurie hours. The radon seeds are inserted by means of long trocar needles, and are placed in position by direct vision through a well-lighted proctoscope. Anesthesia for implantation is seldom required, and patients remain in the hospital only a few days.

Surface applications of radium, with employment of the fractional dosage technique, have been used in a small number of cases in place of gold seed implantations. The rectal applicators required for this type of treatment are fashioned after the ordinary proctoscope and placed in position by direct vision. They are constructed so as to protect the normal rectal mucosa with an additional lead filter whose thickness corresponds to one-half the diameter of the applicators. Daily dosages varying from 100 to 250 millicurie hours have been administered at 0.75 to 1.2 centimeters from the surface of the tumor. Daily treatments are continued for periods varying from three to six weeks with a total dosage of 2000 to 5000 millicurie hours. Although this type of surface irradiation by the fractional method is still in the experimental stage,

the results so far obtained suggest the continuation of its employment in certain types of rectal and anal cancer.

Supplementation of the physical agents by colostomy, or snare removal of redundant areas of tumor, is sometimes advisable. In a few cases, redundant areas of low grade cancer which protrude into the lumen and interfere with radon applications, are removed with the electric snare, after completion of external treatment. Anesthesia is seldom required for this minor operation and patients are confined to hospital for only one or two days. Colostomy is no longer routinely employed with irradiation of rectal cancer. Comparatively few operable cases, treated in this manner, are benefited to any great degree by short-circuiting the fecal stream. An artificial anus is reserved for a few advanced border-line cases, when obstructive symptoms are troublesome, and for a few patients in whom an abdominal opening facilitates the implantation of radon.

SURGERY

Perineal resections, which are well withstood by the majority of poor risks, are routinely employed for cases which are unsuitable for radiation therapy alone. Occasionally, with a high-lying tumor, a graded abdomino-perineal operation is advisable. In the majority of our cases, perineal resection has been preceded by an abdominal colostomy. An artificial anus on the abdomen is more easily cared for than one in the perineal region. Moreover, such an opening often permits a wider dissection. Very obese patients, in whom the construction of a colostomy is a major operation, and those who refuse to submit to such a procedure, are operated upon without preliminary colostomy. Dissection in all cases should be wide, with removal of as large a section of the rectum and as much of the adjacent tissues as is possible. Wide resections are withstood as well as those of a limited nature, and offer greater possibilities of permanent clinical cure.

Operative fatalities in poor surgical risks can be reduced to a minimum by careful preoperative preparation and detailed postoperative care. The former consists in eliminating intestinal intoxication and of improving the general condition by the use of saline cathartics, selected diets, liver extract, tonics, etc. The benefit of such treatment is readily manifest by an increase in appetite, feeling of well-being, etc. Practically all of our poor risks receive preoperative external irradiation. The period required for external therapy affords an excellent opportunity for close observation of the case, and permits the employment of the above measures to good advantage.

The benefit derived from blood transfusions in poor surgical risks can scarcely be over-estimated. All patients receive one or more transfusions before operation and a number have received as many as three during early convalescence. A liberal supply of blood appears to prevent or lessen the severity of shock and the many complications frequently encountered following radical operations. In all probability, more poor risks die of complications than from the shock of the operation itself. Careful nursing is also essential. The liberal use of hypodermoclysis, intravenous injections of saline and glucose, together with administration of digitalis in certain cases of

cardiovascular disease, appears to have helped greatly in preventing postoperative fatalities.

RESULTS

Results following the above forms of treatment in poor surgical risks are encouraging. From 1931 to 1935 inclusive, 39 of the patients treated in our clinic were classified as poor surgical risks. There were 17 male and 22 female patients. 22 were treated by radiation therapy and 17 subjected to perineal resection.

Of the 17 patients surgically treated, 15 had abdominal colostomies and 2, perineal resections without preliminary colostomy. Convalescence was stormy in 8 instances, with one postoperative death. Six patients that survived the operation died of cancer. The length of life varied from six months to three years and eight months. Of the 10 remaining, 9 are well and considered clinically free of disease for periods varying from one and one-half to four and one-half years. The tenth patient is still alive, four and one-half years after treatment, but has a large liver and symptoms suggesting metastatic disease.

22 patients were selected for radiation therapy. Colostomies were constructed in two instances. Redundant areas of tumor tissue were removed with the electric snare to facilitate radon applications in six cases. Results to date in these 22 patients may be summarized as follows: one—poor, four—medium and 17 good results. The poor result occurred in a man who lived but eight months; the cause of death is un-

known, but is thought to be due to disease or to over-treatment. Medium results were obtained in two patients who died with disease three years and ten months, and four years respectively, after treatment. The two other patients are living. One female was free of disease for more than four years, but recently developed a recurrence. The other, a male, has disease two and one-half years after treatment.

Of the 17 good results, to date, one patient died of coronary thrombosis without any evidence of cancer two years and eight months after treatment. The remaining 16 patients are alive and considered clinically free of disease, 5 of whom have passed the four and one-half year period. The periods of freedom from disease of the remaining 11 patients vary from one and one-half to four years.

CONCLUSIONS

Early diagnosis is the greatest asset to successful treatment of rectal cancer. A fair percentage of poor surgical risks with operable disease may be successfully treated by radiation therapy, and retain a normal or practically normal functioning rectum. Cases unsuitable for radiation therapy are best treated by one of the less radical forms of rectal dissection. The choice of treatment rests with the accessibility, size and degree of infection of the primary cancer. Operable mortality may be kept comparatively low by selective surgery and by careful preoperative and post-operative care.

A Practical Method of Analyzing the Precipitating Factors Producing Peptic Ulcer

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IF one were to attempt an analysis of the various theories propounded to explain the etiologic factors responsible for peptic ulcer, he would find himself lost in a maze of conflicting ideas. The literature is self explanatory, i.e., no unanimity of opinion exists in the minds of the investigators regarding the etiologic basis of this ever increasing medical problem.

It is not the purpose of this paper to attempt to reduce the chaos to order nor to complicate the situation further by adding another theory. Rather, it is our idea to outline a practical means of office investigation by which one may determine the precipitating factors, producing a gastro-intestinal upset.

An appraisal of the most frequently mentioned etiologic factors responsible for gastro-intestinal symptoms arising from peptic ulcer will serve as an introduction to the subject of this article. These are summarized excellently by Rivers (1) into four groups: 1. Neurogenic factors. 2. Circulatory disturbances. 3. Erosion of tissue by acids. 4. Inflammation and infection. These factors working alone or

together may be responsible for the production of peptic ulcer. It seems reasonable that the interaction of all the factors may be the precipitating cause.

For over a century, the belief has been widespread among physicians that prolonged emotional activity and psychic trauma exert a powerful influence on the production and oft times prevent recovery from peptic ulcer. Cushing (2) quotes Rokitsky as being the first to teach that there was an interaction between the nervous system and the gastro-intestinal tract which under adverse conditions resulted in ulceration. Robinson (3) in a well controlled work advances his proofs in defense of the psychogenic origin or exacerbation of peptic ulcer. He believes that an imbalance in the vegetative nervous system provides the exciting unfavorable stimuli which lead to the production of peptic lesions. Although his article was criticized by Bonta (4), the fact remains that many "inquiring minds" still adhere to the theory that the nervous system is the keystone in the arch of etiologic factors.

Ivy (5), whose clinical experience is corroborated

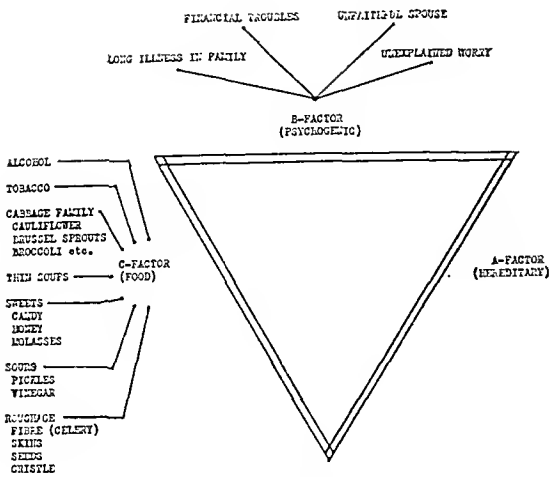


Figure 1

Fig. 1. Analytic chart.

by physiologic experimentations, realizes "the rather important role played by sustained anxiety and associated unhygienic eating habits in the genesis of peptic ulcer." The premise, that the central nervous mechanism, which is responsible for the psychic inhibition of the motility of the stomach, may be conditioned, may also be important in the analysis of the productive factors. It has been shown by reliable investigators that hyperacidity of the stomach is always present in the anxiety complex and in a patient consciously or subconsciously nervous but not afraid.

It is evident from the cursory review of the current theories that despite criticism against the neurogenic origin it is yet the most constant of them all. In a careful study of the food habits of patient with ulcer compared to normal control persons, Elder and Emery (6) were not convinced that quantitative nor qualitative food factors exerted any role in producing peptic ulcers. This well controlled work however does not detract from the value of a well arranged dietary regime in the treatment of peptic ulcer because a well arranged, non irritating, low residue diet is the foundation upon which the treatment is built.

Although studies in the heredity have not clearly demonstrated that there is a transmitted tissue susceptibility in peptic ulcer, such may be assumed because there seems to be a correlation between body build, personality, etc., and this common gastro-intestinal lesion.

A satisfactory uncomplicated procedure has been employed by us in an office practice of gastro-enterology. It provides an excellent graphic explanation of the fundamental reasons or possibilities working alone or together which are responsible for the patient's symptoms. It facilitates the psychologic examination, which, is important not only in the diagnosis, but also in the treatment of peptic ulcer.

We have constructed two charts each containing an equilateral triangle the sides of which are represented by letters A-B-C. A, representing the hereditary factor, B, the psychogenic factor and C, the food factor. The first chart (Fig. 1) represents the diagnostic or analytical chart and is constructed with the apex of the triangle downward which symbolizes im-

balance. This demonstrates to the patient the mechanism of his recurrences and recurrences by the ease with which this triangle may be thrown off balance. After a routine history and physical examination has been completed and a clinical diagnosis of peptic ulcer has been confirmed by fluoroscopic and X-ray examination, the first chart, (Fig. 1), is shown to the patient. It is then explained, that in our theory, the cause of peptic ulcer may be projected on the sides of the triangle. The A side of the triangle is the hereditary factor and is dismissed by explaining to the patient that he has an inherited susceptibility to peptic ulcer. The B side of the triangle or that representing the psychogenic factor, in our experience, may be divided into four main divisions as follows: 1. Long illness in the family. 2. Financial troubles. 3. Unfaithful spouse. 4. Unexplained worry, i.e., a problem which to the patient is unsurmountable and which causes continued anxiety or apprehension. The C side of the triangle represents the food factor, i.e., foods that in our estimation are harmful to a patient with peptic ulcer. Although it has been mentioned previously that the food habits of people with and those without peptic ulcer are practically the same, we feel that the third side of the triangle is necessary to complete our hypothesis.

After this survey has been made with the patient, we then return to the B side or the psychogenic factor. Here, enough time is taken to elicit and identify with one or more of the four subdivisions, the particular inciting agents responsible for the presenting complaint. Careful and oft times repeated questioning will, reveal the psychic stimulus which by constant repetition produces the onset of his disease or a recurrence. It is often not possible to elicit this information at the first visit, but we have found that the graphic charts have facilitated an earlier dissolution of the "reserve wall" with which the patient has surrounded himself consciously or subconsciously.

The second chart (Fig. 2) has been designated the therapeutic chart in which the triangle is constructed with the base downward representing stability. The sides of the triangle are labeled in the same manner as those of Chart 1. Thus, the one factor which is within our control is the food factor, hence it has been established as the base of the triangle. The remaining two sides or factors are explained as follows: On the assumption that there is a hereditary trend in peptic

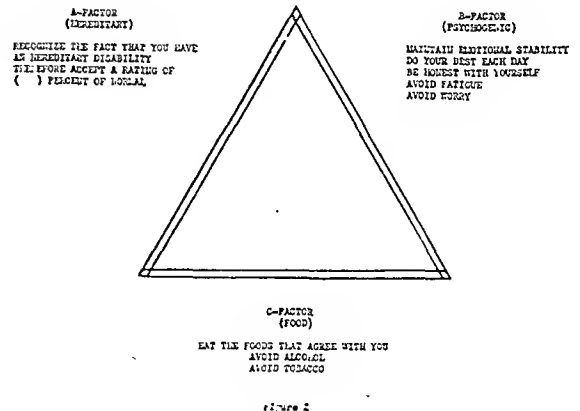


Fig. 2. Therapeutic chart.

ulcer the patient must accept this and try to live within this limit of ability. For example, if he is 25% disabled by his disease, he must strive to live 100% of the 75% and not more.

The psychogenic side of the triangle is discussed and the patient is urged to seek possible solutions for the anxiety which he may have. If, however, the problem is of such magnitude that it cannot be dismissed with ease, he is cautioned to accept a philosophic view and do the best he can each day, be honest with himself, avoid fatigue and worry.

COMMENT

We have presented a workable office procedure for the study of the causes and the possibilities of treat-

ment in peptic ulcer. We believe that this method is a simple and satisfactory one and it is our impression that the successful treatment of an ulcer depends upon the determination of the underlying psychogenic factor. When this factor has been discovered and freely discussed with the patient then the treatment is well on its way. We found that this method has greatly supplemented the usual diet and alkalization treatment.

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Editorials

TESTING OF THE SECRETORY ACTIVITY OF THE GASTRIC GLANDS IN MAN BY MEANS OF HISTAMINE AND INSULIN

UNTIL recently all test-meals used for determining the composition of human gastric juice and for studying the course of its secretion had a common defect, namely, that one could never obtain a pure gastric juice with their aid. The juice was always contaminated with the food substances employed in the test, and with saliva and duodenal juices, or it was diluted with the solutions of those special substances (e.g. alcohol, caffeine, etc.) which were introduced into the stomach for the purpose of stimulating gastric secretion. In an article published in this Journal (Vol. 4, p. 392, August, 1937) Wilhelmj fully discussed the difference between the *gastric contents* and the *gastric secretion* and pointed out that it is a mistake to draw conclusions from the former with regard to the acidity values of the latter. However, there were further disadvantages attending the use of these test-meals, the chief being that in a diluted and contaminated gastric juice no direct determinations could be made of its acidity, or its enzymatic power, or of the concentration of its organic and inorganic components and of its mucus content.

The introduction into clinical practice of the *histamine gastric test* has made it possible to study the course of secretion and the composition of practically pure gastric juice in human subjects. It is sufficient to remember how many patients, diagnosed as cases of "achylia gastrica" on the basis of the results obtained with ordinary test meals, have shown themselves able to respond with a secretion of gastric juice to histamine. As a test of the secretory function of the gastric glands, however, histamine has its limitations. It has been demonstrated repeatedly in animals and man that histamine stimulates particularly the parietal cells of the gastric glands, and moreover in appropriate concentrations inhibits the activity of the peptic cells. (For literature, etc., see my article in this Journal, Vol. 5, p. 107, April, 1938). Gastric juice obtained through histamine administration in experimental animals possesses very high acidity, a very high concentration of total chloride and extremely low peptic power, as well as a low con-

tent of visible mucus. In man the histamine gastric juice has also a very high acidity, but the concentration of pepsin in it varies from one case to another and determinations of the enzymatic power of this type of juice do not furnish reliable data concerning the function of the peptic cells of the gastric glands. Therefore, being one of the strongest stimulants of the parietal cells, histamine may be used with great advantage in medical practice whenever it is desirable to determine the ability of the stomach to produce hydrochloric acid. No correct information concerning other components of the gastric secretion (pepsin, dissolved mucin, visible mucus) could be obtained from analysis of samples of this juice. Thus the hopes of the clinicians that with the histamine test reliable information concerning the function of the gastric glands in man could be obtained were not fulfilled.

Fortunately we possess another substance, namely, insulin, subcutaneous or intravenous administration of which provokes a copious secretion of gastric juice in animals and man. (For literature, etc., see my article on "The triple mechanism of the chemical phase of gastric secretion," appearing in the October number of this Journal). The composition of the gastric juice obtained with insulin differs from that of the juice elicited by histamine. The acidity of the insulin juice is only a little lower than that of the histamine juice, and the concentration of the total chloride is as high in the former as in the latter. But in addition the insulin juice possesses strong peptic power and contains a fairly large amount of visible mucus. In other words, insulin stimulates not only the parietal cells, as histamine does, but also other secretory elements of the gastric mucosa, namely, the peptic cells, the chief cells of the neck and the surface epithelium cells. This fact indicates that with insulin a different mechanism is involved in stimulating the secretory apparatus of the stomach than in the case of histamine. And indeed it has been proved that insulin, by producing hyperglycaemia, stimulates the vagal gastric secretory centres in the brain; the impulses from the brain are transmitted along the vagi to all those secretory elements of the gastric mucosa which they innervate. Section of the vagi or administration of atropine prevents insulin from exerting its secre-

tory effect on the gastric glands. Histamine, on the other hand, acts directly on the parietal cells, which is evident from the fact that the secretory effect of histamine is not at all, or only partly, inhibited by atropine (Gray, *Am. J. Physiol.*, Vol. 120, p. 657, 1937).

The extraordinary importance of the fact that insulin stimulates the gastric glands through the parasympathetic nervous system moved us to obtain first-hand information concerning its secretory effect. Dr. D. R. Webster in our laboratory studied this problem on a dog with esophagotomy and a gastric fistula before and after double intra-thoracic vagotomy. Five units of insulin (Connaught Laboratories, Toronto), injected intravenously, were used to stimulate gastric secretion. Before vagotomy had been performed, the secretion started about 35 to 40 minutes after the administration of insulin. By this time the blood-sugar level usually had fallen to 68-66 mg. per cent. If the blood sugar fell below 50 mg. per cent, a 20 per cent solution of glucose (150 cc.) was introduced intravenously. The gastric juice obtained by means of insulin injection in all respects resembled a typical vagal juice (e.g. that obtained by sham-feeding). It possessed high free and total acidity and strong peptic power. The effect of insulin was easily arrested by a small dose (2 mg.) of atropine sulphate. After vagotomy, as several experiments revealed, insulin was absolutely ineffective in spite of the great reduction of the blood sugar which accompanied it. On the other hand, histamine produced its usual secretory effect (see table below).

Gastric Secretion	Before Vagotomy March 3 5 units insulin	After Vagotomy (performed April 8)	
		April 29 5 units insulin	May 3 0.5 mg. histamine
Total volume (cc.)	103	129	2.7
Duration (hours)	2½	1½	3¼
Free HCl (m.eq./l.)	130	139	53
Total HCl (m.eq./l.)	141	146	107
Pepsin (Mett units)	217	0.4	27
Lowest blood-sugar concentration (mg. %)	52	—	50

On the basis of the physiological data presented above we may evaluate correctly the special importance of various gastric test-meals and select an appropriate one for a definite clinical purpose.

(1) It is advisable to use histamine in cases where it is desired to ascertain whether the stomach of a patient is able to secrete hydrochloric acid, and if so in what amount, for example in suspected cases of achylia gastrica or cancer.

(2) The insulin test may be employed whenever it is necessary to determine the magnitude of the first, or vagal, phase of gastric secretion. The ordinary test-meals (tea and bread, oat-meal gruel, etc.) usually consumed by the patient with no great pleasure cannot supply the necessary data. Yet it may be very desirable in the case of peptic ulcer or a contemplated operation on the stomach or duodenum to find out whether there is, or is not, any hypersensitivity of the vagal secretory apparatus. An excellent description of

the application of insulin to the study of gastric secretion in man may be found in a paper by Welin and Frisk (*Acta Med. Scandinavica*, Vol. 90, p. 543, 1936). The work of the Swedish investigators is the more valuable since they employed a double gastro-duodenal tube and by continuous suction of the duodenal contents prevented their contaminating the gastric juice.

(3) The histamine and insulin tests for gastric secretion may be relied on to furnish the clinician with all necessary information as to the functional state of the gastric glands. If continuous suction is applied to the gastric contents, as has been done by Welin and Frisk, the course of the secretion and the volume of the gastric juice can be easily determined. Incidentally the continuous suction of the gastric juice will prevent the possible irritation of the gastric or duodenal mucosa with undiluted gastric juice in the presence of peptic ulcer. However, the histamine and insulin tests do not give any information concerning the motility of the stomach. The ordinary test-meal (e.g. oat-meal gruel), by which the time of evacuation from the stomach can be determined, serves well for this purpose, especially if it is rendered opaque so that its passage to the duodenum may be watched on an X-ray screen.

If more detailed particulars are required concerning the course of the secretion of hydrochloric acid by the stomach and its partial neutralization by the duodenal juices, a special test-meal, e.g., 2 per cent Liebig's extract, as advocated by Wilhelmj *et al* (see the review by Wilhelmj, Finegan and Hill in this Journal, Vol. 4, p. 457, 1937) may be employed. However, like all test-meals where the gastric juice is mixed with the substance introduced into the stomach, Wilhelmj's test-meal has the usual defect, namely, that the investigator can never obtain a pure gastric juice in which he can determine not only the acidity but also the pepsin, the dissolved mucin and the mucus content.

It seems likely that the histamine and insulin tests of the functional ability of the gastric mucous membrane, owing to simplicity of performance and the exactness of the data which they provide, will in the future replace other types of gastric test-meal now in use.

B. P. Babkin, Montreal.

To the Editor:

DR. W. Lloyd Adams has called my attention to a misstatement in the article by Dr. Rutherford and myself which was published in the American Journal of Digestive Diseases and Nutrition for October, 1938, entitled, "Studies on the Use of Aluminum Hydroxide Gel in the Treatment of Peptic Ulcer." The statement was made, "Also, it has been stated (6) that the secretion of acid does not return to former levels for several weeks after the discontinuance of the aluminum hydroxide" and the basis for this was attributed to an article by Einsel, I. H., Adams, W. L. and Myers, V. C. in the American Journal of Digestive Diseases and Nutrition, 1:513-516, Sept., 1934.

This is not correct. The latter authors wrote merely that, "The free acidity of the stomach is lowered after treatment with aluminum hydroxide, but returns to the initial level after the medication is discontinued."

Naturally, Dr. Rutherford and I regret exceedingly that this error should have occurred and will appreciate having this letter published in the Journal.

Edward S. Emery, Jr.

Book Reviews

The Wheel of Health: A study of a very healthy people. By G. T. Wrench, M.D. (Lond.). C. W. Daniel Company, Ltd., 40 Great Russell Street, W.C.1, London, England. 6 shillings (\$1.50 plus 12 cents postage).

THE study of disease indicates an interest in health, since the attainment of the latter is the object of the former. The author of this book throughout his earlier years aspired to approach the health problem directly by studying carefully and in detail, people who possessed unusual health. This aspiration naturally did not greatly impress those erudite gentlemen whose function it was to sanction the subject for his thesis, with the result that Wrench fell back into the groove of standardized medical pursuits during his productive years as a practitioner, but he did not forget his innate bent, and returned to it, with avidity, only recently. With a clarity of vision, never found disassociated from great sincerity, he has captured what has the appearance of being a story of the most healthy people living in the world at present—the Hunza nation. His acceptance of the Hunzas in this role is based on exhaustive enquiry, description, reference, and comparisons, which easily persuade the reader of the validity of the claim. It is shown first of all that, actually, the Hunzas do not become ill—disease is almost unknown in their valley and among their 14,000 inhabitants. Then it is proved fairly conclusively that this happy state of unique physical fitness (old men of 70 play strenuous polo and retain the characteristics of youth) is to be attributed to their diet. The latter is low in meat, but rich in dairy products, whole grain cereals, germinating seeds, fresh vegetables, abundance of freshly picked fruit and freshly fermented wine. Not too great a variety is eaten at any one time. This diet, it will be seen, is high in "protective" substances, and resembles the ideal diet of McCollum and Simmonds, although the latter did not mention wine. The limitation of varieties at any one meal is rather a new conception, save for the teaching of certain American food fadists, which has not received the sanction of the profession. This all sounds like a simple prescription, in view of the fact that the people who eat it, and because they eat it, fail to furnish any of the exhaustive catalogue of diseases which adorn the repertoire of the European and American practitioner. Not even appendicitis? No, not even a single spastic colon, and no concession to the Western luxury of "allergy." What a benighted race indeed. But, as Dr. Wrench quickly points out, it is not quite so simple as it appears. As usual there is a catch in it. Just as the reader has seized a pen to make a list of the "Hunza diet" (which might be used on himself if not his patients, and procure for him a prolongation of his mortal itinerary) a difficulty looms up. He might eat the Hunza diet but he cannot obtain it. Those fruits, vegetables, cereals and germinating seeds are intangibly different from ours because they are the products of mountain terrace farming and each edible product today has a history through its seeds—a history in Hunza of the most expert agricultural tradition, in which soil fertilization is attained by special use of special composts. It

is almost inferred that the plain love of agriculture is not unconnected with the brilliant food results long attained in this mountain nation.

What is the moral? Merely this—that if any nation could duplicate the Hunza's agricultural fine accomplishments, and then, as a body, partake of these farm products at once after removal from the soil, and in the same balance as the Hunzas do, that nation would, in a reasonable time, enjoy freedom from practically all diseases. Is the problem of health, and particularly the problem of disease really so simple as that? Naturally one would infer not, but Wrench has so carefully controlled his findings, that logically at least he is not wrong in his conclusion.

I regard this book as one of great potential importance. Even if its main thesis might be discovered somehow to be unjustifiable, it marks an acknowledged turning point in medical interest: for why ought not a great deal of attention be directed to the study of normal health and, as here, supernormal health? Again, this book indicates, as an increasing number of books do, the intrusion of the philosophy of "wholeness" into the speculative phase of the science of medicine. Not only has our emphasis been too exclusively on the negative aspect of health, but we have been unjustified in assuming that the full prescription for health was duly supported by the multifarious agencies of society. Thus to assume that the vegetables and cereals eaten by our patients would do them good was right, but to assume that these particular products would give the utmost in physical health, was unjustified without some kind of control over the agricultural agency.

"The Wheel of Health" will probably fail to create an immediate revolution in medicine, because few if any books have ever done so, and because the attainment of the Hunza ideal, like all worthwhile ideals, is full of related problems over which no definitive profession or group of thinkers can at once exert control in any considerable degree. To physicians with the hobby of farming, it should be possible at least to put some of Dr. Wrench's ideas to the practical test, even though such test must be of a limited character. Finally, this work shall not have failed in its general intent, if it succeeds in familiarizing us with the tremendous advantage, long ignored, of directing at least part of our attention to the normal and the supernormal.

Beaumont S. Cornell, Fort Wayne.

Le Diagnostic Radiologique du Cancer de l'Estomac au debut. By René A. Gutmann. (Report to International Congress of Gastro-enterology, September, 1937). Jean Vromans, Bruxelles, 1937, 133 pages.

GUTMANN is one of the best gastro-enterologists in Paris. He is a charming, well-educated man who is in charge of a large gastro-enterologic clinic. It is a delight to find someone writing on the early diagnosis of cancer of the stomach. Too often in the past writers have described the patient who is in the terminal stages of the disease. Gutmann bases his

diagnosis on serial films, since he believes that it is impossible to diagnose cancer in its earliest stages fluoroscopically. At this point many American roentgenologists would disagree with him. He believes that once a man becomes conversant with these earliest changes, there is no great difficulty in making the right diagnosis.

Gutmann recognizes three early forms of gastric cancer: first, the infiltrating form in which the principal sign is rigidity of the gastric wall; second, the ulcerating form in which the principal sign is the niche; and third, the vegetative form, in which the principal sign is the filling defect.

The infiltrating form makes itself known by a rigidity of a segment of the gastric wall which is usually somewhat depressed. At times, when both sides of the prepyloric region are infiltrated, the pylorus has a conical contour, the so-called "sugar-loaf pylorus." Occasionally the cancer shows itself as a flat, rigid area with two straight or curved slopes at the ends. The French speak of this as the "aspect encastré" or "fitted in" appearance. This form may be complicated by the addition of a niche. At times there may be little undulations which are fixed, forming the "corrugated iron pattern."

Gutmann wisely points out that a cancer can look just like an ulcer. In the earliest stages such an ulcer may appear to heal under treatment, and the patient may become symptom free for several months. Sometimes cancer grows in one sector of the wall of the ulcer. It is a joy to find Gutmann saying "Contrary to certain modern opinions, this transformation is frequent; . . . once in five times in ulcer does not heal because it is in a stage of malignant transformation."

Gutmann is not much interested in the ulcerated cancer because this so often represents a late form of the disease. He describes in detail the appearance of the plateau-like niche which he feels is characteristic of cancer. There are also what he calls "big triangular niches." Gutmann speaks also of the "meniscus sign" of Carman, which he believes important but not pathognomonic. Cancer may begin also with a niche that cannot be distinguished from that of ordinary benign ulcer. In these cases Gutmann relies for diagnostic help partly on the therapeutic test.

In differentiating benign from malignant ulcers, Gutmann relies on a number of points. Ulcers are more likely to be malignant when situated on the horizontal than on the vertical part of the stomach, and they are far more likely to be malignant on the greater curvature. Gutmann is not quite so fearful of large niches as are the men at The Mayo Clinic. "The progressive development of irregularities in the floor of the niche should make one highly suspicious of malignancy." Gutmann learns much also from the appearance of the gastric walls around the ulcer. However, there is no sign which is absolutely pathognomonic. The hypermotility of hypomotility or hypertonicity or hypotonicity of the gastric wall is not of value in diagnosis.

In his therapeutic tests Gutmann uses intravenous proteinotherapy, and if the lesion is benign, he expects to see a rapid reduction in the size of the niche. Its persistence is a suspicious sign, and any increase in size indicates the presence of cancer. Diminution in the size of the niche will reassure, but it is not positive proof of the benign nature of the lesion. The disappearance or the approach to disappearance of the niche is the best criterion of the benignness of the

lesion. Gutmann doubts if the niche of a really malignant ulcer ever disappears.

With the proliferating type of cancer the earliest changes result in an irregular outline of the pyloric canal, or slight peculiarities in the contour of the lesser curvature, or irregular, thickened, interrupted, or "embossed" shadows of the rugae. One must distinguish if possible between benign tumors and poly-poid gastritis. Some of the early cancers closely resemble benign tumors radiologically. Benign tumors can also become cancerous.

The little volume is well illustrated, and it has summaries in English, German, Spanish and Italian.

"German for Students of Medicine and Science."

By W. F. Mainland, of the Department of German, King's College, London. Price 8 Shillings. Pp. xlvii and 160. London: Oliver and Boyd, 1938.

THIS book is designed for the use of those who, having an elementary knowledge of German, wish to increase their ability to read German scientific literature. It is neither a formal grammar nor a beginner's manual.

In the introductory section the author presents some notes on grammar and suggestions on reading. This portion of the book suffers a little from enforced brevity and an effort to cover linguistic problems that range from possible confusion of "Aus" and "Auf" to the complexities of sentence structure. There is, however, much useful information condensed into these few pages.

The main portion of the work is devoted to short and graduated selections for reading. These are suitable for class work or self-instruction. Numerous footnotes serve as a guide to grammatical construction and idiomatic usages. Many of the selections possess definite literary and linguistic interest but one may offer the criticism that insufficient effort seems to have been made to include passages from current technical journals in order to afford training in scientific terminology and word frequency. The final section is devoted to a large and complete vocabulary which makes it possible to use the book without resorting to a separate dictionary.

This volume is well planned and its material well presented. It possesses definite instructional value and should be of great assistance to those seeking a means of "brushing up" in their German. This assistance, however, is of a general nature. In the opinion of the reviewer, the book does not offer as much guidance as its title implies to those wishing to familiarize themselves with technical medical German.

Henry J. Tumen.

A B C of the Vitamins. A survey in charts. By Jennie Gregory, Baltimore, The Williams and Wilkins Company, 1938, 93 pages.

THIS little book presents in an attractive way much information in regard to the accessory factors of the diet. The material is presented in the form of drawings, diagrams and charts. There are also a few maps showing the distribution over the world of the principal centers where the several avitaminoses are commonly met. There are a number of charts showing the synthesis of the several vitamins.

This is a useful book to have around a dietitian's office where patients and students are being taught.

Abstracts

THE AMERICAN COLLEGE OF PHYSICIANS WILL MEET IN NEW ORLEANS, LA., MARCH 27-31, 1939

The Twenty-Third Annual Session of the American College of Physicians will be held in New Orleans, with general headquarters at the Municipal Auditorium, March 27-31, 1939.

Dr. William J. Kerr of San Francisco, is President of the College and will have charge of the program of general scientific sessions. Dr. John H. Musser of New Orleans, has been appointed General Chairman of the Session, and will be in charge of the program of clinics and demonstrations in the hospitals and medical schools and of the program of round table discussions to be conducted at the headquarters.

BARTELS, ELMER C.

Liver Function in Hyperthyroidism as Determined by the Hippuric Acid Test. Ann. Int. Med., Vol. 12, No. 5, pp. 652-674, Nov., 1938.

The clinical observations and study of the structural changes in the liver in cases of hyperthyroidism have been referred to in the literature for some time. The number of different hepatic function tests have corroborated the impression that there are varying degrees of liver impairment in thyroid disease. With all this evidence at hand to show the increasing importance of the liver in hyperthyroidism a study was planned to investigate this subject by a new method.

The liver function was determined by the hippuric acid excretion test suggested by Quick. When a normal individual takes 6 gms. Sodium Benzoate by mouth 3 gms. of hippuric acid are excreted in the urine in 4 hours.

This study is based on the results of liver function determinations in 148 cases of clinical hyperthyroidism, all of which came to operation. 78 cases had primary hyperthyroidism permitting a subtotal thyroidectomy, 39 had primary hyperthyroidism requiring a two-stage operation, and 31 cases had adenomatous goiter with hyperthyroidism permitting a subtotal thyroidectomy. Liver function determinations were obtained periodically as follows: On the day after admission; on the day prior to operation (8 to 14 days being taken for preoperative treatment); and on the 6th or 7th day postoperatively. The cases requiring a two-stage operation had determinations prior to the

second stage (six weeks usually elapsing between operations) and on the sixth or seventh day post-operatively. All cases did not have the entire series of tests. Determinations were obtained in 12 cases three months postoperatively when they returned for their usual three months metabolic check-up.

Bartels concludes that there is a reduction in the liver function as

shown by the hippuric acid test in a high proportion of cases of hyperthyroidism, only 18 cases out of 148 having a normal response to the test. The degree of change in the liver function was in direct relation to the severity, but not to the duration of the hyperthyroidism. Improvement of the liver function occurred during preoperative treatment and three months postoperatively in cases with

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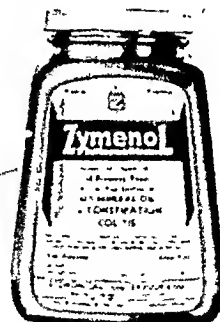
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primary hyperthyroidism. No apparent change was noted in adenomatous goitre with hyperthyroidism. The use of a high carbohydrate diet apparently improves the liver function.

A close relationship was found to exist between the blood cholesterol and the hippuric acid excretion.

B. B. Vincent Lyon and
C. Wilmer Wirts, Jr.

SNELL, ALBERT M.

The Treatment of Liver Disease.
Ann. Int. Med., Vol. 12, No. 5,
pp. 592-608, Nov., 1938.

The essential requirements in the

treatment of parenchymatous hepatic disease appear to be the maintenance of optimal conditions to allow for the regeneration and repair of the parenchyma of the liver.

The observation that a high carbohydrate diet has a definite, specific, protective effect in a variety of experimental hepatic lesions has been substantiated many times. Difficulties in the absorption, storage and utilization of vitamins may also be an element of great importance in the progression of hepatic disease, and their administration by injection has been recommended. The protective effect of Xanthine and Sodium-Xanthine on the liver is noted.

Patients having pancreatic atrophy and presumably a fatty liver were aided by the administration of the hormone "Lipocaic"; notably by the disappearance of ascites and edema and a reduction in the size of the liver.

Although complete proof of the hypothesis is lacking it is justifiable, tentatively, to assume that the syndrome of "hepatic insufficiency" is fundamentally dependent on the failure of the mechanism of detoxification. The management of hepatic insufficiency depends, primarily, on the maintenance of an adequate quantity of carbohydrates, the administration of a sufficient quantity of fluid to dilute and eliminate toxins and the correction of hypoglycemia, anoxemia or hemoconcentration, if these happen to be features of the cases under consideration.

Glucose and chlorides are best given intravenously, and the anoxemia and concentration of hemoglobin at a normal level are assisted materially by repeated small transfusions.

The disturbances between the hydrastatic pressure in the portal-venous system and the colloidal osmotic pressure of the serum, plus some injury to serosal surfaces, are considered the etiological factors in the production of ascites. On this basis the treatment of ascites is directed toward (1) improvement of the condition of the liver, (2) decrease of the portal-venous pressure and (3) elevation of the concentration of proteins in the plasma, thereby increasing the colloidal osmotic pressure of the serum.

Surgically, omentopexy, partial enterectomy and vena-peritoneostomy have been tried. Reinjection of ascitic fluid and relatively high dietary intake of proteins; transfusions of whole blood and plasma and the administration of solutions of acacia, intravenously, have all been of help in some cases. The intravenous administration of amino-acids, the intramuscular injection of liver, the feeding of concentrations of vitamin, have been of definite value. Diuretics should be used cautiously and if ineffectual should be discontinued.

Hemorrhage associated with liver disease may be of two distinct forms: (1) that which results from rupture of collateral circulatory channels and (2) that which is dependent on some intrinsic change in the coagulation properties of the blood. The control of the first situation is a surgical problem, and splenectomy or direct ligation of the coronary veins of the stomach has been attempted as a means of controlling the bleeding. The second situation, so-called "cholemic" bleeding associated with diseases of the liver, is attributable to a deficiency of pro-thrombin which, in turn, is attributable to failure of



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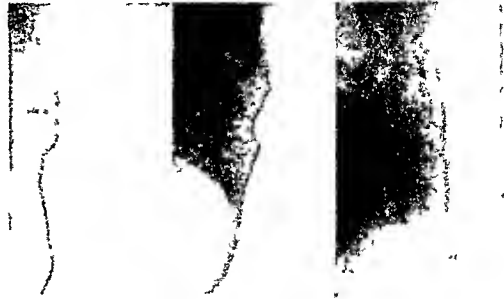
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feedings, useful in peptic ulcer is, stir quickly one envelope (approximately 8 grams) of Knox Gelatine in $\frac{3}{4}$ of a glassful of drinking water and have patient drink quickly before it "sets" or gets lumpy.

*Windwer and Matzner, *Am. Jl. Dig. Dis.*

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absorption or utilization of some substance normally present in the diet which requires bile for its absorption. This substance appears to be the hypothetical coagulation vitamin, (Vitamin K).

NB. An excellent bibliography is appended to this article.

B. B. Vincent Lyon and
C. Wilmer Wirts, Jr.

IHRE, BENGTE.

Human Gastric Secretion. Acta Medica Scandinavica, Supplement XCV, 226 pp., Stockholm, 1938.

Ihre has made careful quanti-

tative studies of the enzymes, acidity, and total chlorides in the gastric juice of 24 normal and 76 pathological cases. For this study he emphasized the importance of a choice of method in obtaining specimens which would prevent, (1) loss of juice through the pylorus, (2) add mixture of duodenal juice due to regurgitation in the stomach and (3) add mixture of saliva. He used, therefore, two Rehfuß tubes combined in the double tube of Lagerlöf and Agren. With this tube in place he could obtain gastric and duodenal juices quantitatively separately. The juices have been fractioned in 20 minute periods, although occasionally the interval was

10 to 15 minutes. Histamine and insulin were used as stimuli for their experiment.

These studies were limited to gastric and duodenal ulcers, chronic gastritis and finally pernicious anemia.

On the whole individuals with gastric ulcers showed a normal rate of secretion, while in most of those with duodenal ulcer there was more or less marked hypersecretion. In chronic gastritis without ulcer the tendency was clearly toward hyposecretion. Higher degrees of acidity than normal were not observed and he concludes that the concept on hyperacidity lacks actual foundation. The majority of the pathological cases showed lowered acidity than normal. This is due to the great effect of the acid-reducing factors in the pathologically altered stomach. These factors are the diluting effect of increased secretion of mucus and the increase back diffusion of acid due to alteration of mucous membranes. A correlation between total chloride and acidity was noted in which when the acidity declined or disappeared the chlorides do not fall below 120 m. eq. per liter. Lower values are unquestionably due to add mixture of saliva. In insulin hypoglycemia the normal cases showed an average pepsin concentration two or three times greater than occurred during histamine stimulation.

Howard F. Root, Boston.

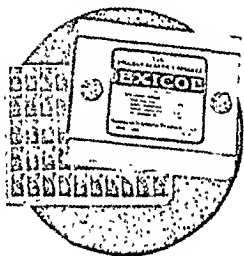
BABKIN, B. P.

The Abnormal Functioning of the Gastric Secretory Mechanism as a Possible Factor in the Pathogenesis of Peptic Ulcer. Canadian Med. Asso. Jour., 38, n.s., pp. 421-429, 1938.

Babkin feels that under certain circumstances the process of gastric secretion may deviate from its course and conditions may arise which lead to destructive processes in the mucosa. To understand how this may occur he first reviews the physiology of gastric secretion.

Histamine is a stimulant of gastric juice; it stimulates the parietal cells specifically, highly acid, has the maximum total chloride, and is poor in pepsin and mucin or mucus. Babkin asks rhetorically whether histamine forms part of the normal mechanism of gastric secretion. He shows that histamine juice and sham-feeding juice are alike except for greater pepsin and total organic substances in the latter. He quotes Hollander as saying that the parietal cells alone are able to concentrate the chlorides as above the blood level and Miss Toby as showing that almost all the water of gastric juice is secreted by the parietal cells. In achylia gastrica the volume of juice is meagre, the

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*Amer. J. Digestive Diseases, Vol. 5, No. 6, p. 348, August, 1938.

**J. Lab. and Clin. Med., 19:567, 1934.

Constipation with Spasticity

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(Stearns)

In order to determine the therapeutic efficacy of Mucilose in the treatment of constipation, clinical studies were conducted in a series of spastic colitis cases because in this disorder it is imperative that no substance be given which would irritate the sensitive colon.

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Most of the patients had obtained

only temporary relief from the use of cathartics, enemas, induced emesis, or from taking alkaline powders for reflex pyloro-spasm.

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chloride concentration low, and the acidity nil, yet the peptic power of the juice is great. He hypotheates therefore that the parietal cells are stimulated to action by histamine or a histamine-like substance. Histamine is very abundant in the stomach walls and mucosa is also found in the gastric juice obtained by any method—sham feeding, vagal stimulation, or histamine injection—in the same concentration although the concentration of the histamine-equivalent varied with the rate of secretion. The histamine in the gastric juice is probably secreted by the mucosa rather than filtered from the blood since the

venous and arterial histamine are the same during gastric activity, while the gastric juice concentration increases. Also, the blood histamine is found mostly in the formed elements rather than in the filtrable elements. He concludes therefore that histamine is conveyed into the gastric juice in conjunction with the secretion of the acid producing cells. The action of the vagus nerve on the gastric glands is through the mediation of acetylcholine which is directly on the peptic cells. These cells liberate histamine in conjunction with other secretory products. The parietal cells are

stimulated through the mediation of histamine liberated from the peptic cells.

In normal gastric secretory processes during which histamine is liberated there are inherent possibilities of pathological disturbances which may lead to ulcer. As well as acting on the parietal cells, histamine acts on the blood vessels, especially the capillaries, causing a paralysis and increased permeability so the whole plasma can pass through leaving the capillary packed with formed elements. This sort of stasis has been observed and differs from actual standstill of the bloodstream because there is plasma exudation into tissue and clumping of blood cells in the capillaries. Diapedesis of red cells may also occur.

In prolonged stasis in the gastric mucosa the part deprived of its blood supply becomes devitalized and necrotic. When the mucosa only is affected an erosion occurs which has frequently been observed after large histamine doses or strong vagal stimulation. It is a long way from mucosal erosion to peptic ulcer, which is relatively rare compared to the frequency of erosion. But in certain areas of the stomach the thinness of the gastric mucosa, the less abundant blood supply, the more abundant nerve supply, and the greater exposure to mechanical factors favor the conversion of local circulatory disturbances into a major lesion of the gastric wall. In short histamine is not the sole cause of ulcer formation, nor does ulcer invariably begin through a disturbance of circulation in the gastric mucosa, but this is just one possible mechanism in peptic ulcer formation.

Edward E. Jemerin.

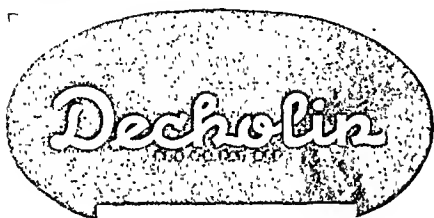
MARTIN, LAY.

Some of the Recent Biochemical Concepts of Gastric Secretion and Their Application to Clinical Medicine. Ann. Int. Med., Vol. 12, No. 5, pp. 614-623, Nov., 1938.

This paper summarizes the data in the investigation of changes in the acid-base pattern of human gastric secretion, the secretory concentration of hydrochloric acid and of the neutral chlorides; to determine, if possible, the type of cell, or cells, secreting these neutral chlorides; and to study the inorganic phosphates during various stages of secretion. The nature of the protein and non-protein portion of the gastric juice and a different method of titrating gastric secretion, with the interpretation of the significance of these data in their clinical sense, is submitted.

CONCLUSIONS AND SUMMARY

When gastric secretion stimulated by histamine begins, a fluid of chang-



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ing acid-base equilibrium is secreted into the normal stomach. The element common to these changes is chlorine which is always found in the gastric juice. Appropriate stimulation will cause it to be secreted into the stomach in greater concentration than in the resting juice, and any significant increase in the chlorides is accompanied by an increase in the titratable acidity. It will often be accompanied by an increase in the volume of hydrochloric acid whose concentration in the extracted juice varies inversely with that of the fixed base (neutral salts). In human gastric secretion the absence of

neutral salts has not been noted. Chloride concentration of the gastric juice equal to the total electrolytic strength of the serum has been found. In the majority of instances the former was below this level. The question of the monocellular source of the chloride secretion remains an open one.

The human gastric juice also contains a protein, gastro-globulin, which has been crystallized and is closely associated with pepsin and urease. There are one or more protein-like materials present and one or more of these have carbohydrate molecules attached. In this juice there are also

such materials as ammonia, urea, uric acid and amino acids whose concentrations in the normal and certain abnormal individuals usually fall within predictable limits.

The term, "combined acidity," is considered as incorrect and for clinical purposes the titration of gastric juice should be carried out to an end point with Töpfer's solution, approximately pH 3.8, since at this point practically all of the acid chlorides both as hydrochloric acid and protein chlorides have been determined.

It is believed that gastric analysis should not be resorted to as a routine diagnostic procedure but that it should be performed only in those cases in which information concerning the secretion is of importance.

B. B. Vincent Lyon and
C. Wilmer Wirts, Jr.

HESLOP, T. STEWART.

The Nervous Control of Gastric Secretion. An Experimental Study. British Jour. of Surgery, 25, 884-899, 1937-8.

Heslop undertook two series of studies in an attempt to determine the neurogenic factors in peptic ulcer.

In the first group (recovery experiments), using stomach tubes and either cats or dogs, a preoperative gastric analysis and histamine reaction was first obtained. One of our procedures was then performed, 1. bilateral splanchnectomy, 2. celiac ganglion excision, 3. bilateral vagotomy, 4. bilateral splanchnicotomy and vagotomy. The operations were found in no way to permanently influence the acidity of the juice or the rate of flow. Immediately after vagotomy there was a lower normal acidity, but this became normal again in a month. The histamine response remained unchanged nor was it affected by any procedure on any of the vegetative nerves. This is because the action of histamine is on the parietal cells alone. The value of histamine as a test of gastric function is therefore small.

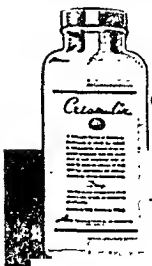
In the second group (acute experiments), cats were mainly used; a tube was first inserted into the stomach through the duodenum and then the drops of juice were collected through a drop counter. Electrical nerve stimulation was applied at the rate of 50 impulses per second, this rate being found most effective in producing changes. The experiments lasted 6 hours or more and then the animal was sacrificed. In splanchnic nerve stimulation either above or below the diaphragm the results were the same. In 3 to 5 minutes there was a diminution in flow or even a fading out of gastric secretion. On cessation of the stimulus, the flow returned in 1 to 2 minutes. This he felt was a



NON-ALKALINE THERAPY IN GASTRIC HYPERACIDITY

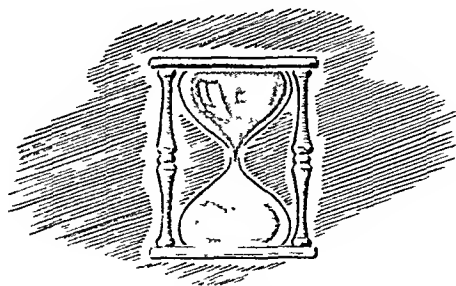
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vasoconstrictor effect. However, there was also noted a rise in acidity above the resting level. Mucus appeared in the juice and the free acid fell while the combined acidity rose. In all experiments, on cessation of splanchnic, vagal, or celiac stimulation the free acid continued to rise for a while, as though it had to reach an equilibrium before it could be stopped. In splanchnic stimulation this was felt to be due to the parasympathetic content of the splanchnic nerves and with atropinization there was a sharp fall in acidity which further splanchnic stimulation was ineffectual in raising

again although the mucus secretion was greatly augmented. The splanchnics and the vagi are mixed nerves, the admixture occurring central to the thorax since cats with vagotomy still had enough vagal content in the splanchnics to influence the acidity.

Stimulation of the celiac ganglion did not influence the rate of flow quite as readily as when the splanchnics were stimulated and the acidity was raised to a higher degree. After atropine, the behavior was the same as in the splanchnic experiments; the acid fell and coelica ganglion stimulation was more effective in depres-

sing the flow of juice but had no effect on the acidity. This less marked effect is due to the large vagal component of the coeliac axis reaching it through the celiac branch of the posterior vagal trunk.

On vagal stimulation, after a 3 to 5 minute latent period there was an increase in flow and acidity. This was appreciably higher than on splanchnic stimulation and tended to persist after the cessation of stimulation.

In hypothalamic stimulation a Souttar machine emitting impulses at the rate of 50 per second was used. A rectangular area demarking the projection of the hypothalamus on the brain surface was marked out. Two sensitive points were found in this area, one at the anterior end, the other at the posterior. On stimulation of the anterior point, after a latent period usually of 6 minutes though sometimes as long as 15, there occurred a sustained increase in the flow of gastric juice accompanied by an increase in acidity. After stopping the stimulus, the increased flow persisted for a variable time and then relapsed. The response was very much like that on vagal stimulation. On stimulating the second, posterior, sensitive point the response was not as certain and definite as at the anterior point although when a change occurred it was always of the same nature. After 6 to 10 minutes the flow of juice slowed and stayed slow until the stimulus was stopped. There was then a slow return to the pre-stimulation level. Also there was an increase in mucus and a decrease in free acid. Here the response was a pure sympathetic one. When vagotomy was performed at the usual level anterior hypothalamic stimulation still caused an increase in the flow of secretion and the acidity though not as much as in the non-vagotomized animal, indicating that the vagi in small part reached the stomach through an alternate route. As far as the author could determine, the hypothalamus between the anterior and posterior sensitive points was silent as far as gastric secretion was concerned.

The formation and secretion of mucus, he concludes, is in part, at any rate, under nervous, (sympathetic) control.

Edward E. Jemcrin.

HOLLANDER, FRANKLIN AND JEMERIN, EDWARD E.

Preparation of Stomach Pouch Without Interruption of Vagal Supply. Proc. Soc. Exp. Biol. Med., 39, 87, 1938.

In a previous publication (see preceding abstract) it was shown that both the ventral and dorsal trunks to the dog's stomach run symmetrically with one another along the lesser



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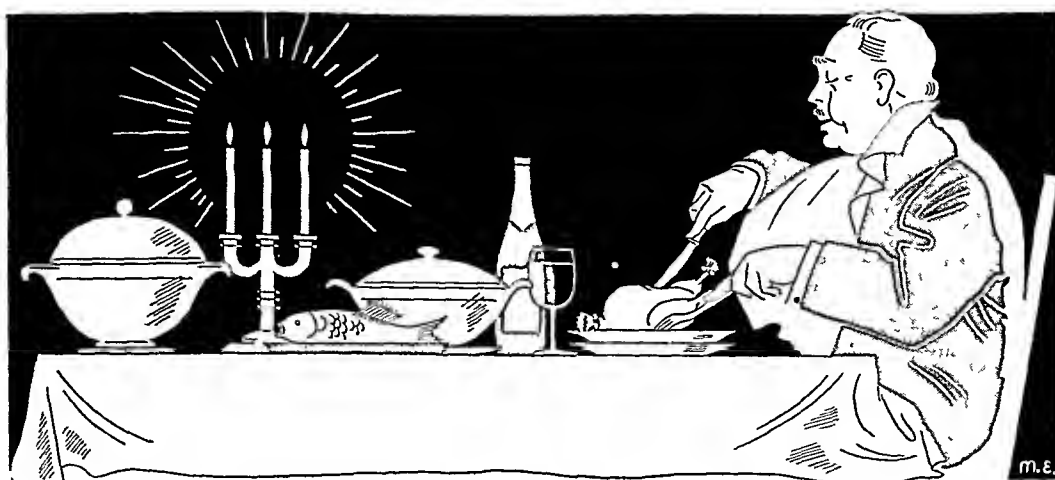
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curvature. Branches from the main trunks pass transversely to the long axis of the stomach. This is contrary to the concept of the vagal anatomy of the dog's stomach held by Pavlov and the Pavlov pouch which was made on this anatomical basis, therefore, lacks the bulk of its vagal supply.

A gastric pouch with uninterrupted vagal innervation was devised as follows: An incision is made through all the layers of both anterior and posterior gastric walls from a point on the greater curvature, about 1 inch proximal to the end of the pyloric antrum, to about half way across the stomach walls. This incision runs parallel to the vagal branches. From

the ends of this incision, mucosal incisions are extended in the direction of the long axis of the stomach to their point of projection on the greater curvature where they unite. Mucosal flaps about $\frac{3}{8}$ of an inch in width are dissected back on both the stomach and pouch sides of the mucosal incisions. The flaps on the stomach side of the incision are sutured to each other, as are those on the pouch side. The stomach is then completely closed off by suturing together the stomach aspect of the initial incision. Similarly, the pouch aspect of the initial incision is closed off, leaving, however, a small opening at its greater curvature angle for the pouch mouth. The pouch mouth is

then brought up through a small counterincision in the abdominal wall.

Edward E. Jemerin.

CHEEVER, DAVID.

Innocent Gall Stones or Harmful Cholecystectomy. New Eng. Jour. of Med., Nov. 10, 1938.

Dr. Cheever feels that there is no such thing as an innocent gall stone or a harmful cholecystectomy therefore: all gall stones are potentially harmful and should be removed since cholecystectomy itself can be attended by a very low mortality rate.

Some of the statistics in the literature quote the incidence of gall stones in routine consecutive autopsies as 32.5 per cent and the presence of cholecystitis in 59.6 per cent of cases. He cites a number of personal cases wherein he feels operation at the time when the disease was first diagnosed would have diminished the hazard attending later operation.

He feels that the gall bladder symptoms following a pregnancy indicate cholecystectomy. To further his contention, he analyzes 109 operative fatalities in gall stone disease seen at the Peter Bent Brigham Hospital. In half of these cases there was sufficient warning to enable an early diagnosis to be made and operation performed before the occurrence of secondary complications which were the essential causes of the fatalities. With a mortality of .8%, such as he has in primary operations, as contrasted to a mortality of 4.1% where disease had gone beyond the gall bladder and involved the common duct, the advantages of early operation are obvious. He minimizes the possibility of postoperative adhesions and of any physiological disturbance following cholecystectomy.

Henry H. Lerner.

COLCHER, A. E.

New Displacement Technique for Gastric Mucosal Relief. Acta Radiologica, Vol. 29, 5, 615, 1937.

The author uses a Trendelenburg position for studying the mucosal relief of the stomach. The normal barium mixture is used. An adaptable fluoroscope is used, which has head and shoulder rests. Foot straps are applied over the insteps. In this manner, the patient can be kept in position with least amount of discomfort and can be rocked from a vertical position down to a Trendelenburg position of not less than 45 degrees.

Among the routine mucosal pictures the author publishes a case of scirrhous carcinoma, which showed a finely mashed honeycomb appearance of its surface.

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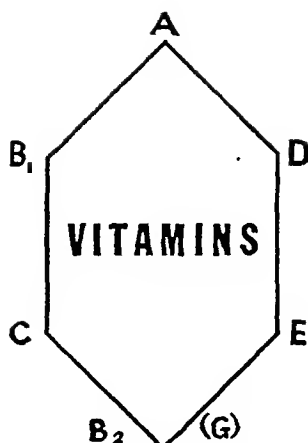
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(1) Copeman, W. S. C., *The Medical Standard*, May, 1930, p. 12.

(2) *New and Non-Official Remedies*, pub. by Amer. Med. Assoc., p. 370, 1938.

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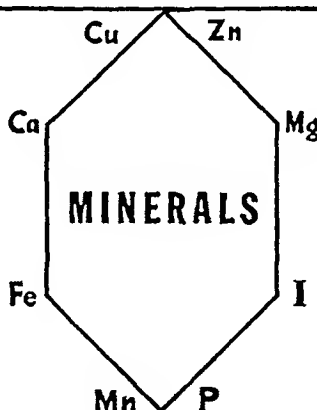
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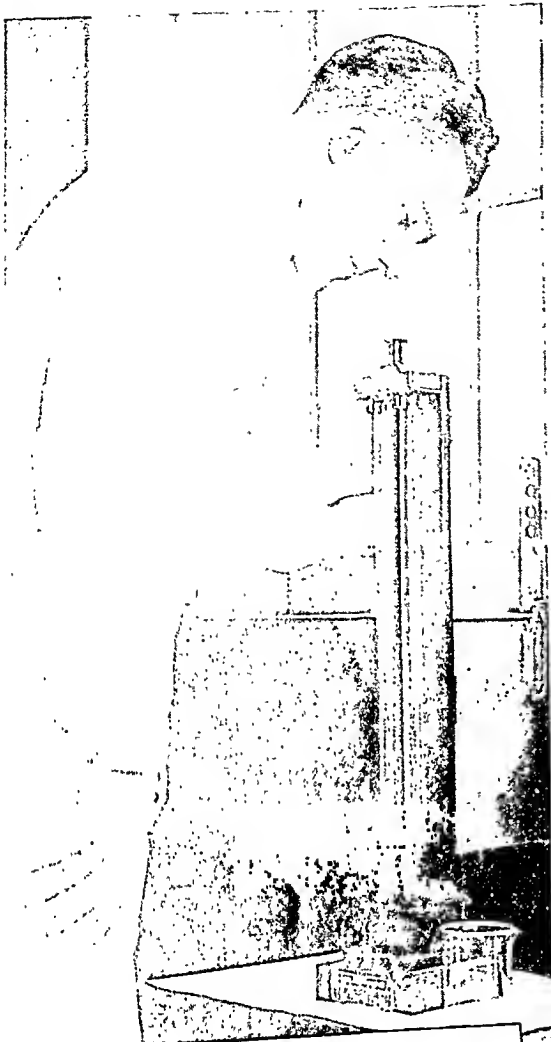
¹Southern Medical J., August, 1938.

²Report of League of Nations Health Committee, Dec. 6, 1935.

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RAVDIN, I. S.

Factors Involved in the Retardation of Gastric Emptying After Gastric Operation. Pa. Med. Jour., 41, 695-700, 1938.

Fluoroscopic evidence of the failure of the stomach to empty after reconstruction or short circuiting operations cannot be accepted as evidence that a mechanical defect of the anastomosis exists which will permanently retard normal gastric emptying. Under most favorable circumstances, a newly made stoma may not function for some days after operation. Fortunately, evidences of retention disappear in most cases, and gastric lavage affords relief until the stoma gives evidence of functioning.

The author then analyzes the following factors which have been held responsible for persistent post-operative vomiting:

1. Presence of bile and alkaline duodenal juices in stomach. This is disproven by well-being of patients after cholecysto-gastrostomy.
2. Spur at anastomotic site due to dropping downwards of afferent and efferent loops, producing a sharp kink, thus directing fluid from afferent loop into stomach. The incidence of this factor has been greatly reduced recently by suturing the bowel to the stomach for some distance on either side of the stoma, avoiding acute kinking.
3. Anti-peristaltic implantation of jejunum (as in original Wolfier operation) probably over exaggerated as a factor since such an operation in the dog is followed by perfectly normal emptying.
4. Other factors mentioned by various authors are: use of long jejunal loop, valves of gastric mucous membrane, closure of stoma by newly formed adhesions, compression of efferent loop by colon.
5. Recently, intussusception of jejunum was shown to be a cause of stomal obstruction, but occurs some time after recovery from operation, after period of normal gastric emptying.
6. Spasm at stoma site—Ravdin proved results were not encouraging when he used large amounts of drugs, whose primary purpose is relief of smooth muscle spasm. Therefore, if there is spasm, it is of minor importance.

Ravdin advances three other factors:

1. Interference with nervous innervation attending many resection.
2. Presence of edema at anastomotic site (with or without resection) due to trauma.
3. Edema of serum protein deficiency, especially if patient suffers from prolonged dietary deficit, due to: a. prolonged medical regime, b. self-imposed restriction—due to pain or vomiting or both. Coincidental dehydration often masks the hypoproteinemia and the true state is unrecognized until fluids and large amounts of NaCl are given, which precipitate and intensify the edema.

The author claims that edema of truma plus that due to hypoproteinemia together produce sufficient swelling of stomal site to account for more failures of gastric emptying after Bilioth I and II operations than are due to technical defects of anastomosis.

He experimentally produced hypoproteinemia in dogs by restriction in diet and plasmapheresis, keeping protein intake to 1%, but giving sufficient vitamin. As serum protein fell, gastric emptying time prolonged (shown by fluoroscopy) in both operated and unoperated dogs. In man, there is probably also added vitamin deficiency; if due to B₁₂ lack, gastro-intestinal atony results.

Ravdin concludes: 1. Pre-operative serum protein determinations should be done, while fluid-salt balance is being restored. If level approaches critical level for edema, patient should receive 1 or more transfusions of whole blood or serum.

2. Pre-operatively, put Abbott-Rawson tube in stomach. After completing anastomosis, distal valve is drawn into

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Albert Cornell.

JEMERIN, EDWARD E. AND HOLLANDER, FRANKLIN.

Gastric Vagi in the Dog. Erroneous Assumption of Uninterrupted Vagal Innervation in the Pavlov Pouch. Proc. Soc. Exp. Biol. Med., 38, 139, 1933.

According to Khigine and Pavlov, the anterior vagal trunk to the dog's stomach descends the lesser curvature to the pylorus. The posterior trunk, however, descends the greater curvature, to the middle of the pars pylorica. Pavlov devised a gastric pouch on the basis of this vagal anatomy, so that the posterior vagal trunk would descend into the pouch mucosa uninjured. The pouch, with blood and nerve supply intact, would therefore respond to all stimuli with a secretion comparable to that of the stomach proper.

The foregoing nerve distribution differs from that found in the human, where both the anterior and posterior trunks are found to course along the lesser curvature of the stomach. It was therefore thought wise to repeat the dissections in dogs. Dissection of 20 dogs consistently showed Khigine and Pavlov's anatomical concept to be erroneous. A constant architecture was found consisting of the following: On the esophagus the left and right vagal trunks divided into ventral and dorsal branches. The ventral branches united to form a ventral trunk, the dorsal to form a dorsal trunk. The trunks entered the abdomen through the esophageal hiatus in the diaphragm. Both the ventral and dorsal trunks then descended the lesser curvature on their respective stomach surfaces symmetrically with one another to about one inch from the pylorus. Each gave off branches to its respective stomach surface, the branches passing transversally to the long axis of the stomach and disappearing in the musculature about 1/3 of the way across the stomach. No branch was seen to descend the greater curvature as described by Khigine and Pavlov.

Roughly, then, 75% or more of the vagal supply to a Pavlov pouch would be transected by the incisions recommended by Pavlov. While innervation of the entire pouch mucosa might conceivably be effected by microscopic lateral branches or through myenteric

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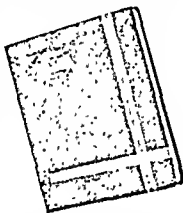
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plexuses, it is equally likely that physiological action would be limited to the apparent sphere of influence, the pouch fundus. In the latter case, one would be dealing with an incompletely innervated pouch, and it might be expected that the response of such a pouch to vagal stimuli would be equally incomplete.

Data available in the literature were insufficient to indicate whether or not Pavlov pouches did respond completely to vagal stimuli despite the anatomical considerations elucidated above. To determine whether there exists a physiological parallel to the observed anatomical deficiency a technique is required for the quantitative determination of degree of vagal response. This must then be applied to Pavlov pouches, to Heidenhain pouches and to pouches which are made according to another technique which will leave the vagal supply uninterrupted.

Edward E. Jemerin.

ROBINS, SAMUEL A. AND ALTMAN, WILLIAM S.

The Significance of the Lateral View of the Rectum. A Description of Technique and its Value. Am. Jour. of Roent. and Rad. Ther., Vol. 40, pp. 593-605, No. 4, 1938.

Re-emphasizing a well known, but too often unobserved detail in roentgenographic studies of the large bowel, the authors present this paper with several illuminating cases. They point out that lesions in the rectum can often be demonstrated in a lateral view; whereas, the routine anterior-posterior view may miss them. This is to a great extent an indictment of the fact that too often we fail to heed the well-voiced dictum that the sole difference between the specialist and the practitioner lies in the fact that the former inserts his finger into the patient's rectum. Any lesion that has obtained a size sufficiently large to produce a defect demonstrable by X-ray ought to be amenable to diagnosis by the digit. The value of the proctoscopic examination is obvious in such instances.

Going beyond their title, the authors show instances of carcinoma of the sigmoid, splenic flexure, and descending colon demonstrated only in the lateral view.

The sole importance of this paper lies in the fact that anyone doing roentgenographic work should not be satisfied with the routine procedure hitherto pursued in studying the colon. The authors suggest that after the usual prone and oblique films are taken that a left lateral exposure be made. In this view, the rectum and sigmoid, which are often obscured by redundant loops of bowel, are clearly visualized. They fail to make mention of the use of the double-contrast enema which in many instances has

proved its value in the diagnosis of single polypoid lesions in the rectum or colon.

Henry H. Lerner.

ZDANSKY, ERICH.

Roentgenological Findings in Achylia Gastrica. Fortschr. a. d. Gebiet d. Roentgenstrahlen, Vol. 56, 5, 635, 1937.

The author describes, besides 2 cases of carcinoma of the stomach, another case, which was observed for 15 years. The patient had an achylia with normal or slightly hypochromic anemia. The X-ray examination showed hyperplasia of the stomach mucosa which was similar to a tumor. The hyperplasia gradually subsided with a decreasing of the clinical symptoms. The author emphasizes that these cases are not too rare.

Franz J. Lust, New York.

ODQVIST, HENNING.

X-ray Findings in a Neurinoma of the Stomach. Acta Radiologica, Vol. 18, 1, 101, pp. 112-118, 1937.

A case of gastric neurinoma is described, which showed clinical signs of bleeding, but otherwise only indefinite dyspeptic discomfort. The roentgenological examination revealed the presence of a well circumscribed tumor with a naval-like niche.

Franz J. Lust, New York.



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The Effect of Anterior Pituitary-Like Hormone on Gastric Acidity in Man*†

By
HENRY FELSON, M.D.
and
LEON SCHIFF, M.D.

With the technical assistance of
ELLEN S. GABER, M.S.
CINCINNATI, OHIO

THE relationship of sex hormones and gonadotropic hormones to gastric acidity in man appears to be one of much interest due to the fact that modal gastric acidity in man is higher than in woman and that acidity is more frequent in the female (Bloomfield). In a previous communication we reported no effect on gastric acidity following the repeated intramuscular administration of estrogenic hormone ("Theclin"). We were eager to determine next the effect of anterior-pituitary-like hormone on gastric acidity because of

were instructed not to swallow any saliva. A Rehffuss tube was introduced into the stomach and the fasting contents were withdrawn. One-half milligram of histamine phosphate‡ was given subcutaneously and continuous aspiration carried out for a total of one hour; the juice collected being divided into ten minute period samples. The volume as well as the acidity of each sample was recorded. The presence of bile and

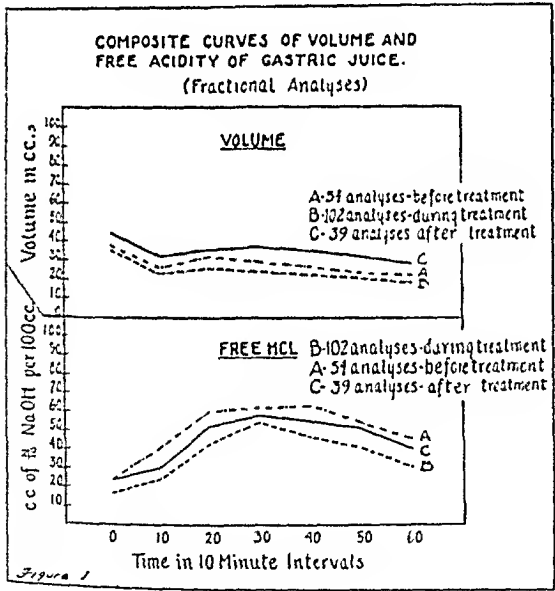


Fig. 1

its gonadotropic qualities. This hormone has been reported by Winkelstein to produce no constant effect on the gastric secretion of the dog.

METHOD USED

Four patients and three controls were selected for study. Three were males and four females. The ages varied between twenty-two and sixty-one years. They all reported to the laboratory in a fasting state. They

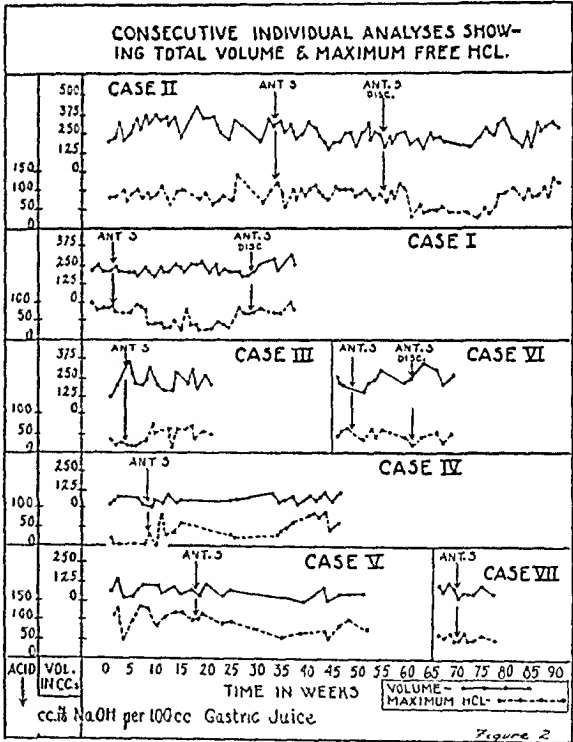


Fig. 2

mucus was noted. Free acidity was determined by the standard method of titrating with N/10 NaOH using Toepfer's reagent as an indicator.

A control period of observation preceded the institution of treatment varying from one week in some cases to eight months in one case and included at least three analyses. In one patient, twenty-four control analyses were performed. Normal acidity was present in three of the subjects, diminished acidity in three and increased acidity in the remaining one. During

*From the Department of Internal Medicine, University of Cincinnati and the Gastric Research Laboratory, Cincinnati General Hospital.
†Study made possible by a special grant from Parke-Davis & Company through the cooperation of Dr. E. A. Sharp.
‡Furnished by Parke-Davis & Company.
Submitted July 31, 1938.

treatment, analyses were usually done at weekly intervals, though in some instances the intervals were longer. After cessation of treatment, weekly analyses were continued for approximately two months in two cases and eight months in a third.

sisted for seventeen and nine weeks respectively. Case 2 showed no change until six weeks after treatment was ended, at which time a drop of fifty occurred which persisted for fourteen weeks. Because this decrease occurred after treatment was discontinued and

TABLE I
Data on patients receiving anterior pituitary-like hormone

No.	Age	Sex	Diagnosis	Duration of Treatment (Months)	Number of Injections	Number of Gastric Analyses	Duration of Study (Months)	Gastric Acidity Before Treatment
1	37	M	Mucous Colitis	7	150	35	14½	Normal
2	43	M	Duodenal Ulcer	5	130	74	21	Normal
3	44	M	Duodenal Ulcer	4½	103	18	4½	Decreased
4	61	F	Chronic Cholecystitis	9½	100	23	11½	Normal
5	30	F	Normal (Castrate)	8	79	22	12	Increased
6	41	F	Normal (Menopause)	1½	33	13	5½	Decreased
7	22	F	Normal	2½	32	10	2½	Decreased
Av	39			5.4	89.6	27.9	10.1	

Injections consisted of 1 cc. "Antuitrin-S"§ given subcutaneously into the upper arm. In most of the patients injections were given daily; however, in two (Cases 4 and 5) treatment was not given regularly because of lack of cooperation. The duration of treatment ranged from 1¼ to 9½ months, the injections numbered 32 to 150 and the duration of study varied from ½ to 21 months (Table I).

A total of 195 analyses was performed. Composite curves of volume and acidity of gastric juice obtained before, during and after treatment are given in Fig. 1. A slight lowering of volume and free acidity occurred during treatment followed by a slight rise after treatment was discontinued. It is felt, however, that the changes are too small to be significant.

Curves of maximum free acidity for any one ten minute collection period (on a given day) together with total volume of gastric juice obtained in the entire one hour periods are depicted in Fig. 2. Volume appeared to be unaffected except for a persistent slight lowering in Case 2 which occurred ten weeks after treatment was begun. It may be seen that two cases (3 and 4) showed an increase of 30 in maximum acidity six and three weeks after treatment was begun which persisted for practically twelve weeks and thirty-five weeks respectively (at which time treatment was discontinued). Two cases (1 and 5) showed a decrease of 30 in acidity nine and eighteen weeks after beginning of treatment which practically per-

was later followed by a rise to the original level, it is felt that it may have occurred spontaneously.

The immediate effects of injections of "Antuitrin-S" on gastric volume and acidity were observed in five patients. Fourteen analyses were done in which the administration of histamine was immediately preceded by subcutaneous injection of 1 cc. of Antuitrin-S without any unusual effect on gastric secretion.

In only one individual receiving repeated injections of Antuitrin-S (Case 6) was any untoward reaction observed. This subject was in beginning menopause and experienced metrorrhagia and dysmenorrhea which became so marked that treatment had to be discontinued.

SUMMARY

The subcutaneous administration of anterior pituitary-like hormone (Antuitrin-S) to a group of seven individuals in daily doses of 1 cc. for a total of 32 to 150 injections produced no constant effect on the volume and acidity of gastric juice as obtained in a one hour period following the subcutaneous administration of histamine.

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§Furnished by Parke-Davis & Company.

Observations on the Incidence and Cause of Fever in Patients* with Bleeding Peptic Ulcers

By

L. V. DILL

and

C. E. ISENHOUR

NASHVILLE, TENNESSEE

KRONER (1) 1926 in a review of the literature called attention to the paucity of comment on the rise in temperature that may occur in patients with peptic ulcer. He pointed out that very little is known concerning either the incidence or cause of this fever.

Table I summarizes the data available in the litera-

TABLE I

Summary of the available data concerning the incidence of hemorrhage and fever in peptic ulcer

Author	Number of Cases	Presence of Hemorrhage	Presence of Fever		
			All Cases	Non-Bleeding	Bleeding
Lorenz	179		24%		
Kroner	300	8%	18%	16%	58%
Bang	358	42%	51%	7%	91%
Purjesz	350	30%			73%

ture on the incidence of fever in patients with peptic ulcers, bleeding and non-bleeding.

Although others had observed that patients with bleeding gastric and duodenal ulcers often had fever (2) Kroner (1) states that Lorenz was the first to study the incidence of pyrexia in such patients. Lorenz reported a series of 179 patients, 21 per cent of whom had fever. Kroner, reporting from Strauss'

TABLE II

The average age, duration of symptoms and sex incidence of the various groups

	All Ulcers	Non-Bleeding Ulcers	Bleeding Ulcers	Gastric Neuroses
Age (Average)	45.07 years	45.38 years	44.02 years	37.56 years
Duration of Symptoms (Average)	8.20 years	8.39 years	7.55 years	6.10 years
Sex Incidence	75% males	74% males	80% males	45% males

Clinic in Berlin, found that 18 per cent of 300 ulcer patients had temperatures which exceeded normal at least once during their stay in the hospital. One year later Bang (3) of Copenhagen, in a study of 358 cases

*The Department of Medicine, Vanderbilt University, School of Medicine, Nashville, Tenn.
Submitted July 11, 1938.

of peptic ulcer personally observed, found that 50 per cent had sustained rises of temperature. He believed that the presence in his series of a relatively large number of active, bleeding ulcers accounted for the discrepancy between his figures and those of the

TABLE III

The incidence of fever in patients with peptic ulcer

	All Ulcers	Non-Bleeding Ulcers	Bleeding Ulcers	Gastric Neuroses
Percentage with Fever	53%	46%	80%	37%

earlier authors. It is to be noted that these figures pertain to all ulcer cases, and that the incidence of bleeding varied greatly in the different groups. In Kroner's series 8 per cent of the patients had hematemesis and of those 58 per cent had fever (at least one temperature observation well above normal). Only 16 per cent of the non-bleeding cases were febrile. In Bang's series hemorrhage was noted in 42 per cent and 91 per cent of these had prolonged rises of temperature, although in a small number of these cases it was impossible to rule out the effect of medi-

TABLE IV

The incidence of fever in relation to varying degrees of hemorrhage

	Massive Hemorrhage	Moderately Severe Hemorrhage	Small Hemorrhage
Number of Cases (44)	22 (50%)	11 (25%)	11 (25%)
Presence of Fever	19 (86%)	9 (82%)	7 (64%)

cation. Only 7 per cent of the non-bleeding ulcer patients were febrile. Purjesz (4) reporting on 380 ulcer patients, found that 30 per cent were bleeding and 73 per cent of these had a rise of temperature above 37.0° C. by axilla.

The cause of fever in peptic ulcer has been variously ascribed to absorption of methemoglobin or blood degradation products, reduction in blood volume, anemia, asthenia or shock with resulting increase in lability of the heat regulating center, and to gastritis. The absorption of blood from the intestinal tract was assigned as the cause of the fever as early as 1887 by

Eichorst. Leichtenstern (5) went so far as give to "absorption fever" the name, "Febris Methematomica." He stated vaguely that it was "a fever that sometimes is quite mild, sometimes rather high, sometimes perfectly atypical, irregular and remittent,

Purjesz (4) found that a definite rise in body temperature occurred following the reduction of blood volume in dogs by bleeding and he produced anemia and fever in dogs with phenylhydrazine. He interpreted these results as indicating that blood loss was a definite

TABLE V
The incidence of peptic ulcers, hemorrhage and fever in relation to age groups

	Bleeding Cases			Non-Bleeding Cases		
	Group 1 0-20 years	Group 2 21-40 years	Group 3 41 plus years	Group 1 0-20 years	Group 2 21-40 years	Group 3 41 plus years
Number of Cases	2	13	24	5	51	99
Massive Hemorrhage	1	9	13	—	—	—
Moderately Severe Hemorrhage	0	4	7	—	—	—
Small Hemorrhage	1	5	4	—	—	—
Presence of Fever	1 (50%)	16 (89%)	17 (71%)	3 (60%)	21 (41%)	46 (47%)

sometimes continuous for several days," and added that it appeared 2 or 3 days after the occurrence of the hemorrhage in association with constipation. Kroner (1) noted that very large hemorrhages were almost always accompanied by fever and that young patients had less fever than the older ones. He considered the size of the hemorrhage the important factor in determining the extent of the temperature elevation. Riegel (11) states that many observers considered fever in peptic ulcer as being due to toxic or infectious material or to a ferment caused by red blood cell destruction. Others believed that the anemia itself caused dysfunction of the heat regulating center. Krehl (11) postulated similarly that the products resulting from the disintegration of red blood cells entered the blood stream and affected the heat regulating center through the vegetative nervous system. He also suggested that anemia alone could cause the fever and cites as evidence the increase in body temperature often seen in pernicious anemia and hemolytic jaundice. Jacobs (11) thought that generalized body weakness could increase the liability of the heat regulating center. Bang (3) felt that the fever could be reasonably referred to the gastritis which accompanies ulcers. The observations of Lange (6), Faber (7), Askanazy (8), Konjetzny (9), Kalima (10) and others indicate that gastritis is not an uncommon occurrence.

factor in the production of fever in patients with bleeding ulcers.

We became interested in the problem after noting that the opinions expressed in the literature were at variance, and that none entirely coincided with the impressions gained from the study of patients in this clinic.

CLINICAL MATERIALS AND METHODS

All cases of peptic ulcer studied in the Vanderbilt Hospital from the year 1925 through 1936 were reviewed, and from these 199 patients with peptic ulcers, proven by X-ray, laparotomy, or both were chosen. Each patient had been observed in the hospital for more than three days and was known, within the limits of error, to have no intercurrent infection.

The material was divided into three groups: Group 1 consisted of 155 patients with peptic ulcers whose stools did not contain occult blood, and who gave no history of recent bleeding. Group 2 consisted of 44 patients whose stools gave strong reactions for occult blood and who had, for the most part, come into the hospital with complaints referable to hemorrhage. A control group (Group 3) was composed of 78 patients with complaints referable to the gastro-intestinal tract, in whom no organic disease could be demonstrated and who were diagnosed as having gastric neuroses.

TABLE VI
The incidence of ulcers, hemorrhage, and fever in relation to the duration of ulcer symptoms

	Bleeding Cases			Non-Bleeding Cases		
	Group 1 0-2 years	Group 2 3-10 years	Group 3 11 plus years	Group 1 0-2 years	Group 2 3-10 years	Group 3 11 plus years
Number of Cases	9	26	9	57	60	37
Massive Hemorrhage	4	13	6	—	—	—
Moderately Severe Hemorrhage	2	8	1	—	—	—
Small Hemorrhage	3	5	2	—	—	—
Presence of Fever	7 (77%)	20 (77%)	16 (89%)	16 (47%)	26 (43%)	19 (51%)

"Fever" in our studies was arbitrarily defined as any rise in temperature above 99.0° F. which was sustained for more than two days, any rise to 99.2° F. or above for two days, or any single rise exceeding 100.0° F. The temperature of each patient was taken

TABLE VII

The incidence of fever in bleeding and non-bleeding ulcer patients with and without anemia

	Patients With Bleeding Ulcer		Patients With Non-Bleeding Ulcer	
	With Anemia	Without Anemia	With Anemia	Without Anemia
Number	14 (31%)	31 (69%)	4 (3%)	140 (97%)
Presence of Fever	13 (93%)	23 (74%)	4 (100%)	64 (46%)

every four hours during the day, and, in the presence of fever, at the same intervals at night. All patients had blood studies on admission to the hospital, including red blood cell counts, white blood cell counts, hemoglobin determinations, and a differential count of the stained leucocytes. In the presence of hemorrhage frequent hemoglobin determinations, red and white cell counts were done. Stool examinations were made in practically all instances when the patients were first admitted to the hospital, and when patients were found to be bleeding, stool examinations were made at frequent intervals thereafter.

The age of each patient was determined by the age given on admission to the hospital and the duration of symptoms was determined from the hospital record.

The amount of diarrhea, vomitus and fluid intake was considered in reviewing the records and particular attention was paid to dehydration. The influence of treatment on the temperature was carefully considered in each instance and all cases in which medication or dehydration was believed to be in part or wholly responsible for the fever were discarded.

The studies on the relation of anemia to the presence of fever in ulcer patients were confined to a group of individuals who had less than 2,500,000 red blood cells or 7.5 grams (50 per cent) of hemoglobin.

CLINICAL OBSERVATIONS

Clinical Data. In order to define clearly the type of clinical material reviewed in this study of fever in peptic ulcer the case histories were analyzed with reference to age, incidence of hemorrhage, duration of symptoms, and sex distribution. (Table II)

In this series the average age of the patients was forty-

five years. The average age of those with non-bleeding ulcer was forty-five years, with bleeding ulcer was forty-four years. The patients of the control group (gastric neuroses) were slightly younger, the average being thirty-seven years. The incidence of bleeding in the ulcer group was 22 per cent.

The average duration of gastro-intestinal symptoms among the patients with ulcer was 8.2 years; in patients with non-bleeding ulcers the average duration of symptoms was 8.4 years, and in those with bleeding ulcers 7.6 years. Symptoms in the gastro-intestinal neurosis group averaged 6.1 years duration.

Males had peptic ulcer three times as frequently as females (75 per cent) in our series and this ratio was maintained in both bleeding and non-bleeding groups. The gastric neuroses showed only a slight preponderance of females (55 per cent).

Incidence of Fever. 106 of the 199 patients of the entire series, or 53 per cent, had fever, temperature elevations which satisfied our criteria for the term. Of 155 non-bleeding ulcer patients there were 71 who had fever (46 per cent). Thirty-five of the forty-four patients with bleeding ulcers, or 80 per cent, were febrile. Fever was present in 37 per cent of patients in the gastric neurosis group. (Table III)

Factors Affecting Fever. In order to see what effect the size of the hemorrhage had on the temperature the cases were classified as examples of either massive, moderate or small hemorrhage. These lines of division were arbitrarily drawn and were none too easily defined, but patients were thus classified on the basis of the impression gained from a complete resume of history, physical examination, and laboratory findings.

The findings in Table IV indicate that in hospitalized patients massive hemorrhages are present or are recognized more frequently than moderate or small ones. Fever as we have defined it is somewhat more commonly encountered and is of longer duration in patients after moderate or large hemorrhages than after small ones.

In order to study the relation of age of the ulcer patients to the occurrence of hemorrhage and fever, the patients were divided into three age groups: 0-20 years, 21-40 years, and from 41 years upward. Table V indicates that the incidence of hemorrhage for peptic ulcer increases with age and that among adult patients fever occurred more frequently in bleeding than in non-bleeding ulcers. The number of patients in the 0-20 year group was too small to permit comparison with the other groups.

An attempt was made to correlate the duration of the ulcer symptoms with the presence or absence of fever. To this end patients were divided into bleeding and non-bleeding groups and each group was separated into three age periods: Those who had symptoms from 0-2 years, from 3-10 years, and from 11 years

TABLE VIII

The influence of fever and hemorrhage on the leucocyte counts of ulcer and neurosis patients

Average Leucocyte Count	All Ulcer Patients	Non-Bleeding Ulcer Patients		Bleeding Ulcer Patients		Control Group (Gastric Neurosis)
	7,871	7,642		7,973		6,975
		afebrile	febrile	afebrile	febrile	
		7,552	7,932	8,224	7,900	

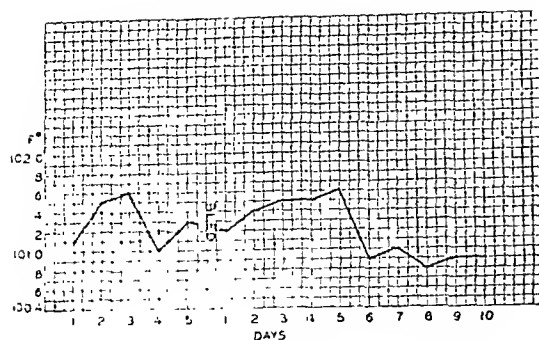


Chart 1. A composite graph, showing the effect of bleeding on the temperature of five dogs.

upward. A study of Table VI indicates that slight if any effect upon the incidence of fever can be attributed to the duration of the ulcer. As in previous charts the effect of hemorrhage on the incidence of fever is noteworthy.

In Table VII it is seen that over 90 per cent of the patients with bleeding ulcers and low hemoglobin values had fever. Four patients with non-bleeding ulcers but with anemia, also had fever. These figures appear to be significantly higher than those for patients with ulcers, bleeding and non-bleeding, but without anemia. Anemia, therefore, seems to be significantly related to the temperature levels exhibited by ulcer patients.

Leucocyte Counts. A comparison of the leucocyte counts in the various groups is noteworthy only because of the absence of significant differences. (Table VIII)

EXPERIMENTAL

Material and Methods. An attempt was made to duplicate in dogs the conditions existing in patients with bleeding peptic ulcers in so far as reductions in blood volume and the presence of blood in the gastro-intestinal tract are concerned and to study the effect of these factors, singly and in combination, upon the temperature of the animals. Dogs of varying size were used and were divided into four groups. In order to determine the effect of massive blood loss on the body temperature, each of five dogs (forming Group I) was bled from the femoral artery one-quarter of its estimated blood volume.* Twenty gauge needles were used and sterile technique was employed. Four dogs (Group II) were given, by stomach tube, blood

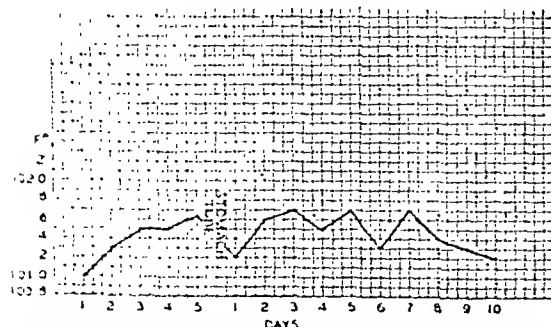


Chart 2. A composite graph showing the effect of giving blood by stomach tube on the temperature of four dogs.

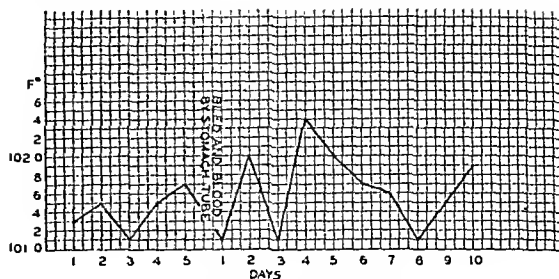


Chart 3. A composite graph showing the effect of bleeding and of giving blood by stomach tube on the temperature of six dogs.

approximating one-quarter of their blood volumes, in an effort to evaluate the role played by blood in the intestinal tract. In order to combine the factors existing in Groups I and II, six dogs, forming Group III, were bled one-quarter of their estimated blood volumes and fed this same blood immediately by stomach tube. Group IV, including five dogs, was used to determine the effect upon the body temperature of the reaction which may occur as the result of arterial puncture. The femoral arteries of these animals were punctured.

Temperatures were taken rectally twice daily (at 8:00 A. M. and 4:00 P. M.) for five days preceding and ten days following each procedure. Only the maximum temperatures for each day are recorded in the charts.

EXPERIMENTAL OBSERVATIONS

Reduction in Blood Volume. The animals of Group I whose blood volumes had been reduced by 25 per cent experienced a rise of temperature, shown in a composite graph (Chart 1) of only 0.1° F. above the control level for that group.

The Presence of Blood in the Gastro-Intestinal Tract. Chart 2, a composite graph of the temperature curves of the animals of Group II which had been fed a large quantity of blood by stomach tube, shows only 0.1° F. rise in temperature above the control level, although this was attained on three separate occasions.

Combination of Blood Volume Reduction and the Presence of Blood in the Gastro-Intestinal Tract. The composite graph (Chart 3) shows the effect of the procedure carried out on Group IV. The temperature of these animals exceeded the highest control level three times, the greatest excess being 0.7° F. However, the observations which follow indicate that this

*The total blood volume was estimated as 1/10 of the body weight.

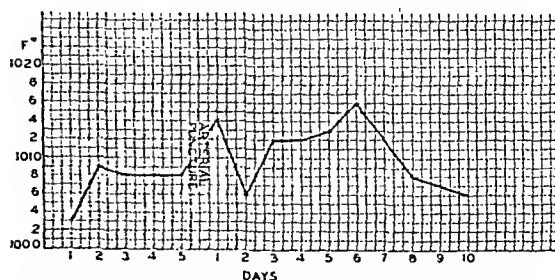


Chart 4. A composite graph showing the effect of arterial punctures on the temperature of five dogs.

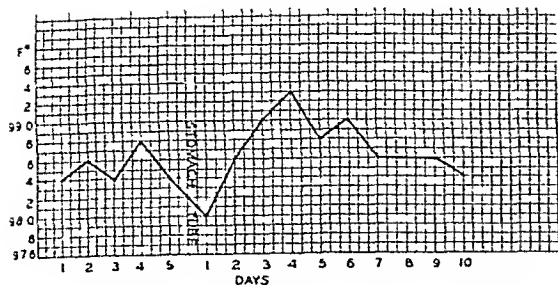


Chart 5, Case 1. The effect of blood in the intestinal tract on the temperature of Subject 1.

temperature elevation was not related to either reduced blood volume or blood in the gastro-intestinal tract.

Control (Arterial Puncture Alone). Following arterial puncture, the post-operative temperatures exceeded the control levels, the highest being 0.7°F . above the maximum for the pre-operative period. This post-operative temperature elevation was maintained for several days. (Chart 4)

In summary it may be stated that under the conditions of our experiment no significant rise in temperature was observed in dogs as a result of rapid and great reductions in blood volume, the presence of large amounts of blood in the gastro-intestinal tract, or a combination of both.

CLINICAL EXPERIMENTS

In order to note the effect of blood in the human intestinal tract upon body temperature, a clinical experiment, similar to the procedure carried out in Group I of the animal experiments was designed.

Material and Methods. The experimental subjects were a young physician and three patients who had been admitted to the hospital with afebrile illnesses and with no symptoms referable to the gastro-intestinal tract. A preliminary control period of five days was used with each patient to obtain temperature records and to exclude the presence of blood in the intestinal tract.

The blood for use in the experiments was obtained by phlebotomy from patients with congestive heart failure. It was collected, citrated, and stored in a refrigerator, under sterile conditions until used.

Moderate doses of morphine and sodium amytal were given the experimental subjects. 500 to 600 cc. of blood at body temperature were introduced into the stomachs of the sleeping patients by Levine tubes.

In order that the blood remain in the intestinal

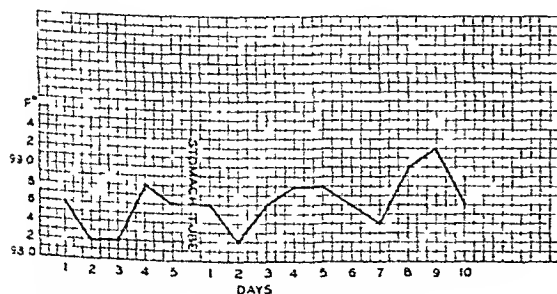


Chart 6, Case 2. The effect of blood in the intestinal tract on the temperature of Subject 2.

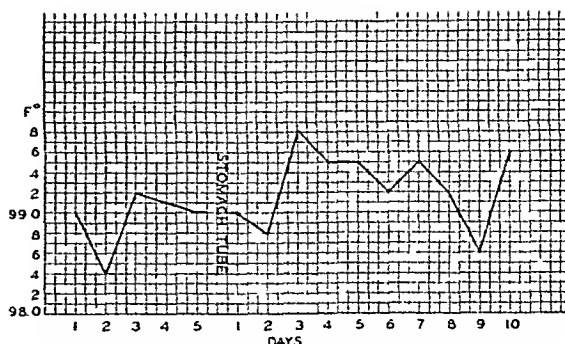


Chart 7, Case 3. The effect of blood in the intestinal tract on the temperature of Subject 3 (see text).

tract as long as possible, paregoric, 4 cc. three times daily, was given for ten days. Temperatures were taken orally every four hours during the day. None of the subjects vomited. Occult blood was demonstrable in the stools from the second to the fourth day after the beginning of the experiment (varying as to constipation) and persisted for from forty-eight to seventy-two hours following its first appearance.

Subject No. 1. K. P., was a forty-three year old white male with multiple sclerosis. After a control period of five days, 600 cc. of blood were introduced into the stomach (Chart 5). Subject No. 2. E. G., was a forty-seven year old white male. The diagnosis was syphilitic aortitis and Adams-Stokes syndrome. After five days of control period, 550 cc. of blood were introduced into the stomach. (Chart 6). Subject No. 3. C. S., was a twenty-one year old white male, diagnosed obesity. Following a four day control period, 800 cc. of blood was introduced into the stomach. (Chart 7). Subject No. 4, a twenty-three year old white male in excellent health was given 500 cc. of blood by stomach tube following the usual five day control period. (Chart 8).

Subjects No. 1 and No. 2 showed only an insignificant rise in temperature following the introduction of blood into their gastro-intestinal tracts. Subject No. 3 did experience an elevation of temperature for the whole period, but it is noteworthy that this exceeded the maximum temperature of his control period by only 0.6°F . Subject No. 4 was afebrile save for one day. On the fourth day following the introduction of blood into the stomach this individual had nausea and vomiting preceded by generalized abdominal pain. After three hours this pain migrated to the right lower quadrant; it subsided seven hours after the onset. Appendicitis was suspected.

While no conclusions can be drawn from such a small

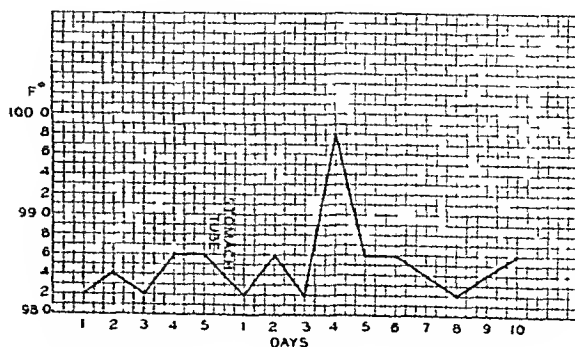


Chart 8, Case 4. The effect of blood in the intestinal tract on the temperature of Subject 4 (see text).

number of observations, we are of the opinion that blood in the intestinal tract of man does not of itself cause a significant rise in temperature.

COMMENT

We have determined the incidence of fever, as we have defined it, in a series of patients with proved peptic ulcers. The incidence of fever in our patients (53 per cent) is identical with the series published by Bang (3), but greatly exceeds those of Kroner (18 per cent) and Lorenz (24 per cent). We found that 80 per cent of our patients with bleeding ulcers were febrile. These figures do not differ greatly from those of Purjesz (73 per cent) or Bang (91 per cent), but are well above those quoted by Kroner (58 per cent). Our percentage of febrile, non-bleeding ulcer cases (46 per cent) is much higher than that of Kroner (16 per cent) or of Bang (7 per cent).

To explain the apparent discrepancy between his figures and those of the earlier writers Bang (3) postulated an increased activity of the ulcers, as evidenced by the high incidence of bleeding in his cases. Using this criterion in an attempt to correlate the incidence of fever to bleeding we are unable to obtain a true parallel by comparing the different series, and interpret the greater part of the variation in figures as to variations in standards of fever. It should be emphasized that we found that patients without demonstrable organic lesion had fever, according to our definition, in a significantly high percentage (37.1 per cent).

We have attempted to relate the fever occurring in patients with peptic ulcers to hemorrhage, the presence of blood in the intestinal tract, the age of the patient and of the ulcer, the presence of anemia, and the leucocyte count. Our series demonstrates that patients with ulcers have fever more frequently than patients with no demonstrable organic lesion, and that bleeding increases this tendency. The presence of anemia also increases this tendency to fever in patients with both bleeding and non-bleeding ulcers. Massive and moderately severe hemorrhages are more frequently associated with fever than are small hemorrhages. We are unable to correlate the occurrence of fever with either the age of the patient or the duration of ulcer symptoms. The absence of leucocytosis in our patients lead us to assume that infection of the base of the ulcer or an associated gastritis or duodenitis is not important in the production of this fever.

The experimental evidence seems to indicate that

little part is played in the production of fever by either blood in the intestinal tract or absorption of blood degradation products.

Our studies throw no light upon the possible influence of a labile vegetative nervous system in the causation of fever, as we have defined the word, but that this may play some role is suggested by the relatively high incidence of fever in patients with gastric neuroses.

SUMMARY AND CONCLUSIONS

Peptic ulcers, bleeding and non-bleeding, occurred most frequently in our series in males of middle age.

The incidence of bleeding in the group of patients admitted to Vanderbilt University Hospital with peptic ulcers was 22 per cent.

Fever was present in 53 per cent of all ulcer patients, in 80 per cent of all patients with bleeding ulcers, and in 46 per cent of all patients with non-bleeding ulcers. In a control group of patients in whom no organic lesion could be demonstrated, fever was present in 37 per cent.

Large hemorrhages were more frequently associated with fever than were the small ones.

The patients with peptic ulcer and anemia had fever more frequently than did those without anemia. Anemia seemed to be significantly related to the temperature levels exhibited by ulcer patients regardless of the presence or absence of hemorrhage.

In our material the incidence of fever could not be correlated with either the age of the patient or the duration of the ulcer.

The withdrawal, under aseptic conditions, of a large amount of blood from dogs does not result in fever. The presence of blood in the intestinal tract of either dog or man does not cause fever *per se*. Indeed, this study does not implicate any single causation factor for the fever which is present in the majority of patients who have bleeding peptic ulcers. It does emphasize the frequent co-existence of fever in ulcer patients with (a) the presence of blood in the gastrointestinal tract and (b) the presence of well marked anemia. The study likewise reveals the frequent occurrence of significant temperature elevations in patients with gastric neuroses. These observations suggest that the incidence of fever may be greatest in patients with bleeding peptic ulcers who have experienced large hemorrhages, are anemic, and have a labile vegetative nervous system.

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The Effect of Pyloric Obstruction on the Filling and Emptying of the Gall Bladder in Cholecystography

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A PERUSAL of the available literature reveals little if any information regarding the effect of delayed gastric emptying in cholecystography. In this brief communication a study of 21 cases of pyloric obstruction, ranging from four to twenty-four hours, with varying degrees of gastric retention has been studied following the administration of tetraiodophenolphthalein. The effect of gastric emptying on the filling and emptying of the gall bladder has been carefully observed. The etiological factors producing the obstruction at the pyloro-duodenal outlet varied, but in the majority of cases ulceration was the principle cause.

The results of filling of the gall bladder obtained in this study is presented in the table below. It will be noted that of the 21 cases, 15 filled normally, as indicated by a dense homogeneous vesicle shadow, while in 6 cases a faint or poor shadow and in 3 a non-filling gall bladder was obtained.

From these studies it would appear that for practical diagnostic purposes, pyloric obstruction is not a significant factor in the causation of non-filling of the gall bladder. Obstructive lesions at the pyloro-duodenal outlet are rarely complete, and since enough of the dye usually flows into the small intestine, incomplete pyloric obstruction should have but little effect upon cholecystography. However, in the case of complete obstruction, in which instance none of the dye passes into the intestine, non-filling of the gall bladder may be observed. This form of obstruction presents a doubtful factor in the non-filling gall bladder which should be borne in mind.

The effect of emptying of the gall bladder has also been studied (see table), following the usual egg-cream-milk meal. In the 15 normally filled gall bladders, 10 contracted normally, i.e. less than half of its original size; while in 5 the size of the vesicle was not appreciably altered. These findings therefore indicate evidence of retardation of emptying in one-third

of the normal gall bladder cases. Our studies on emptying in response to a fat meal would suggest that sluggish emptying in cases of pyloric obstruction has little or no clinical significance.

Of the 3 patients with non-filled gall bladders, 2

Cases	Gastric Retention Hours	Normal Filling	Poor or Faint Outline	Non-Filling	Contraction	
					Normal	Ab-normal
1	4		X			
2	4½		X			X
3	5	X			X	
4	5	X			X	
5	5½	X				X
6	5½	X			X	
7	5½	X			X	
8	5½	X			X	
9	5½	X			X	
10	6	X				X
11	6	X				X
12	6½	X			X	
13	9½	X				X
14	18	X			X	
15	18	X			X	
16	18	X				X
17	18			X		
18	18			X		
19	22	X			X	
20	24		X			
21	24			X		

were surgically explored. In one instance, with a small 18 hour gastric retention, gall stones were found, and in the other case with a small 24 hour gastric retention, the gall bladder revealed pericholecystic adhesions, but was otherwise grossly normal.

History and Development of Gastric Analysis Procedure (Second Installment)

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VI. CONSTITUENTS STUDIED AND ANALYTICAL METHODS EMPLOYED

OF all the constituents of the gastric contents which interest the clinician, the acid secreted by the stomach has always been considered the most important. At first it was thought necessary to know, only in a qualitative way, whether or not free hydrochloric acid was present in the gastric contents. To this end various indicators were employed: congo red, Boas' reagent (resorcinol-sucrose), Guenzburg's reagent (phloroglucin-vanillin), methyl violet, Toepfer's reagent (dimethylaminoazo-benzene), and tropaeolin OO. At the time these various test substances were first introduced the modern physico-chemical concept of acidity was itself very young, and so the literature is replete with discussion of their relative sensitivities. These discussions were concerned with the influence of the various protein degradation products, lactic acid, phosphates, and other buffer substances—as we now designate them—and have continued even as recently as 1914 (Fittipaldi (43)).

It soon became apparent, however, that quantitative estimations of acidity were essential. It is difficult to say just when the titrimetric method was first employed in clinical gastric studies, but as early as 1886 Jaworski and Gluzinski (64) introduced the present system of estimating acidity in "degrees" or, as we now designate it, "clinical units." For these determinations they titrated their specimens with 0.1 N alkali, using litmus as one indicator. Concerning the reagent for titration there is little to say; sodium hydroxide possesses such obvious advantages that it soon replaced the iodometric method of Sahli and became the standard for all subsequent titrimetric work. The proper choice of indicators, however, was a more difficult problem to cope with and it has persisted until the present decade. This difficulty could be resolved only with a clear understanding of the significance of acid-base titration curves and the effect upon them of various buffer substances. Although the early titration work was done with the same indicators which were being used for the qualitative tests, gradually all of these were discarded, with the exception of Toepfer's reagent for free hydrochloric acid, and were replaced by phenolphthalein (e.g., Christiansen (21)). Alizarin for free and litmus for total acidity were also recom-

mended, but by this time they too have been discarded. With the introduction of the pH concept of acidity in 1909 by Sørensen, it became possible to define end-points in terms of those pH units which correspond exactly to whatever definitions of free and total acidity might be adopted. Probably the first efforts in this direction were reported by Michaelis (93) in 1917 and subsequently presented in more detail in a lecture given before the Harvey Society in New York (94). For the free hydrochloric acid end-point Michaelis recommended a pH value of 2.8, which is indicated by a salmon-pink color with Toepfer's indicator; the yellow end-point in general use today is entirely erroneous because it corresponds to a pH value of *circa* 5. For total acidity, he recommended pH 6.5, but as Shohl (125) subsequently pointed out, a value above 7 is more rational because of its proximity to the pH of blood. However, Shohl and King (126) recommended phenolphthalein, the pink color of which corresponds to pH 8-10. For free acidity titrations, they advised thymol blue in preference to Toepfer's reagent, and an end-point of pH 3.0. For routine clinical purposes, Toepfer's and phenolphthalein are probably being used more extensively today than any other combination of indicators. For purposes of investigation, however, particularly where it is important to obtain a reliable evaluation of the combined acidity as a measure of the buffer content of the gastric juice, Hollander (58) has recommended a different combination of indicators: bromphenol blue at pH 3.5, which corresponds exactly to a free acidity of one clinical unit, and phenol red at pH 7.0, which corresponds to exact physico-chemical neutrality and is therefore preferable to the higher value given with phenolphthalein. In order to obtain titration values which are precise to ± 0.1 pH units, the color of the end-point must be determined by comparison with a standard mixture of indicator and buffer solution at the desired pH—a procedure which lends itself readily to precise work with as little as 0.5 ml. of stomach contents and which we are now using routinely in our laboratory for all our clinical as well as animal investigations.

Combined acidity values are determined by the difference between free and total acidities, and are usually small; hence, unless the titrations are performed very carefully and the end-points are sharply defined the results may be extremely unreliable. For

Editors' Note: This is the second installment of this article, the first having appeared in the January, 1939 issue. The Bibliography will be published with the final installment in an early issue.

this reason, as well as the apparent lack of clinical significance, there is a general tendency to disregard the combined acidity (Martin (86), Crohn (26), Wilhelmj (139)) for most practical purposes. On the other hand, with the increasing interest which is now observable in the process of neutralization of gastric contents by duodenal regurgitation and in the non-acid secretions of the stomach, the precise determination of combined acidity may in time become a factor of some significance in gastric analysis (Hollander (59)).

Some mention should be made at this point of the units in terms of which we express acidity. The "clinical unit," or "degrees of acidity" is defined in terms of the number of ml. of 0.1 N NaOH which are titrimetrically equivalent to 100 cc. of the specimen. This definition can be traced as far back as the work of Jaworski and Gluzinski (64) in 1886. In modern physico-chemical parlance, this number is equivalent to the milli-normal concentration (mN). As such, it is more universal, because the same terminology can be applied in expressing the concentration of many of the other factors with which we deal in analyses of the gastro-intestinal fluids. For this reason the latter unit is becoming increasingly popular, and we feel that it should be universally adopted in the terminology of gastric analysis—in preference to "degrees" and "clinical units," and certainly in preference to per cent hydrochloric acid, which offer no theoretical basis for comparison with other constituents like neutral chlorides, total base, etc.

With further extension of the concepts of physical chemistry, it was not long before proposals were made to replace titrimetric determinations of acidity by determinations of pH as such. Within two years after Sorensen had published his definition of pH, Christiansen had already reported the good agreement of titration acidities in terms of millinormal units (using Guenzburg's reagent) with millinormal values calculated from pH values which he determined by means of the hydrogen-gas electrode. Similar comparisons were made by other investigators, though not always with the same results. Thus, Denis and Silverman (31) developed a satisfactory bedside technique which utilized pH test-papers; Shohl and King (126) compared titration and colorimetric pH procedures and obtained better agreement with thymol blue indicator than with Toepfer's, though neither indicator was exact; Kopeloff (73), Norgaard (98) and Vos (138) all reported the correlation between titration and pH values to be far from good. Hence, the latter investigator concluded that not only is the titration method entirely adequate for the purposes of gastric analysis, but it is also the most convenient. A similar conclusion was arrived at by Hollander (58), who pointed out that for free acidity values of the magnitude encountered in gastric analyses, the reliability of an end-concentration in milli-moles when determined titrimetrically is considerably greater than when calculated from a pH determination, be it electrometric or colorimetric. Thus, it is not surprising that pH determinations have been discontinued entirely, for purposes of both clinical and experimental gastric analysis. Furthermore, pH is a more exact physico-chemical criterion of acidity for such phenomena as pepsin activity, but so far as the activity of the acid producing cells of the gastric mucosa are concerned, it is the amount of hydrochloric acid as measured by

milli-normal concentration that is important. Where the color of a gastric sample—due to contamination by bile, for instance—is so great that exact titrimetric determination of a color end-point is impossible, there still remains the principle of electrometric titrations (e.g., see Teorell (134)). By this procedure, the end-point (say pH 3.5 for free and 7.0 for total acidity) is determined with great ease by an electrical method, using the quinhydrone or the glass electrode; but until simple and cheap commercial set-ups are available, it is not likely that this procedure will be adopted for other than experimental purposes.

In addition to the foregoing direct procedures for observing gastric acidity, there have been proposed from time to time a number of indirect methods. As far back as 1877, Szabo (131) utilized the acid hydrolysis of sugar, measured polarimetrically, to demonstrate the presence of free acid in the stomach. In 1908, Holmgren (63) developed the so-called capillary analysis method for free hydrochloric acid in gastric contents. This method was based on the distance to which a drop of acid fluid will spread in a piece of standardized filter or blotting paper, as shown by the presence of an acid-base indicator like congo red. Under properly standardized conditions, this distance is determined by the surface tension relations within the capillary pores of the paper, and these in turn are a function of the acidity. Hence, from the mathematical theory of these physico-chemical relations, it is possible to calculate the degree of acidity which occurs in each case. Unfortunately the values so obtained are in only poor agreement with those derived titrimetrically (Baumstark (8), Key-Aberg (70), Mattisson (90), Schmidt (118) and Orell (99)), and so the method has received almost no attention outside of the Scandinavian countries. In this country Kantor (65) developed a microscopic test based on the swelling of moist collagen fibrils, but this also has found little application. In view of the high quantitative reliability of acid-base titrations and the extreme ease with which they can be performed, it is easy to see why this latter procedure has replaced all others so completely.

Next to the acid content, the pepsin activity of gastric contents has usually been considered of greatest importance. Although qualitative methods were employed for some time before, the first reliable quantitative procedure was reported by Mett in Russian in 1889 and described in German in 1894 (91). It is interesting that, except for the modifications in technique introduced by Christiansen (22) in 1912, this method has been employed almost universally until within the last decade. Neither the refractometric method developed by Schorrer (119) in 1908 and proposed for clinical use by Reiss (111) in 1923, nor the method of Boas (15) which depends on the determination of the amount of starch liberated from a bit of macaroni which has undergone peptic digestion, has ever received much application. Recently, however, as gastro-enterology has become increasingly experimental, there has developed a need for more precise methods of determining peptic activity. In response to this need we now have the highly refined methods of Gilman and Cowgill (49), later modified by Osterberg, Vanzant and Alvarez (101), and of Anson and Mirsky (2). The former depends on the photometric determination of the amount of silver liberated by the digestion of a piece of photographic film, previ-

ously exposed and developed; the Anson and Mirsky method employs hemoglobin as a substrate. Although for investigative purposes we may require a quantitatively more reliable method than that of Mett, the routine purposes of clinical analyses are probably well satisfied by the older procedure. The method of Gilman and Cowgill consumes far less time than the Mett method and for this reason it may ultimately come into more general use.

On the other hand, it is noteworthy that the examination of gastric specimens for peptic activity has never been adopted extensively as a routine procedure, nor by all the signs now apparent is it likely to become so in the immediate future. Similarly with pancreatic lipase and trypsin, which are frequently found in the stomach, although all three of these enzymes are likely to be matters of physiological interest for a long time to come. Phosphate determinations have never attracted any considerable attention because this chemical radical is in no way specific to any secretion or pathological disturbance. In the case of mucus, bile, lactic acid, blood and other cellular elements the situation is different. All of these possess distinct, though not conclusive, significance as diagnostic aids. Thus large amounts of mucin may be indicative of a gastritis, but it may also be derived from the saliva in cases where the latter is excessive. The presence of bile is indicative of duodenal regurgitation, but this is now believed by many workers to be a normal physiological process (Boldyreff (17)); how extensive and important this process is, however, remains a moot question (Shay, Katz and Schloss (124)). Lactic acid is unusually indicative of gastric retention in the absence of free hydrochloric acid. But since it may occur in benign achylia retention as well as in carcinoma involving the pyloric region, the presence of lactic acid is in no way pathognomonic. Occult blood also is no specific indication of hemorrhage due to ulcer or cancer, since it is frequently encountered in superficial erosions and cases of chronic passive congestion (Pilcher (107)). Hence, there have been evolved various qualitative methods for the detection of these several substances all of which can be found in any of the standard works on clinical laboratory procedures. Quantitative methods, however, are not available for any of them, nor is their development likely since knowledge concerning the amounts of these substances is hardly likely to add to the utilitarian value of the present procedures.

Finally, let us consider the inorganic chloride content. Part of this element is secreted as hydrochloric acid, the remainder as neutral chloride from various sources: alkaline secretions of the fundus and antrum, saliva and especially the regurgitated intestinal fluids. Also, it is frequently claimed that in cases of achylia the parietal cells may secrete a fluid which contains neutral chloride and which is the unhydrolyzed precursor of the hydrochloric acid. Hence, although chloride values are no index to hydrochloric acid production, most workers have long felt that the relations between total chloride, neutral chloride and acid chloride might give a clue to the relative extents to which various phenomena are operative in the gastric fluid of any one patient. In order to determine the chloride concentration, any modification of the original Toldard titrimetric method may be employed; the most reliable of these is probably that of Wilson and R. H. (141). Among those who have conducted ex-

tensive studies of the variations in chloride concentration which occur in the course of gastric analyses, we may mention Pfaundler (104); Bolton and Goodhart (18); Baird, Campbell and Hern (5); Holler and Bloch (62); Markoff (85); Gorham, Stroud and Hoffman (53); Rudd (115), and Berglund, Johnson and Chang (11).

As yet none of these workers have been able definitely to correlate secretory disturbances with changes in chloride concentrations, in such a way as to utilize them diagnostically. Even so far as understanding the pathological physiology is concerned, we are still far from grasping their significance. This explains why chloride determinations have found so negligible a place in routine gastric analysis.

VII. PERIOD OF PHYSIOLOGICAL ANALYSIS

In our discussion of fractional analysis above, it developed that the method, though universally accepted, has not come up to expectations, chiefly because of the gradual realization that a simple, precise diagnostic procedure for gastric disease is unattainable. Instead, it has developed that what we must attempt is to study the individual components of the patient's gastric behavior, to compare these with established norms, and from the pathological deviations of these characteristics to build up a composite picture of the stomach which may then serve as a basis for diagnosis. Chief among these physiological components are the emptying time, the response to specific "psychic" and chemical gastric stimuli, the volume of pure gastric juice in contradistinction to the acidity of the stomach contents, etc. Let us, therefore, examine each of these variables in turn, and thus, perhaps anticipate the line of future development of gastric analytical procedure.

A. Emptying Time.

In 1898 Cannon first studied gastric motility and emptying by means of Roentgen rays, and a radiopaque meal for experimental purposes, but clinical use of the X-ray was not initiated until much later. As a consequence of subsequent developments in apparatus and technique, we find today that the observation of the gastric residue, six hours after the ingestion of a barium or a bismuth meal, is being employed universally as a measure of gastric motility. Previous to 1911 all efforts at estimating emptying time had been confined to gross observation of the amount of test-meal which could be removed by means of a stomach tube, say, one hour after its ingestion. In spite of the popularity of the radiographic methods, many gastroenterologists recognized very soon that a motor test-meal yields results which are physiologically and diagnostically more significant than the former procedure (Bassler (6), Levy (78), Bennett and Ryle (9)). Crohn (26) states specifically that in instances of doubt the food test should receive the greater consideration.

Now, if we are to utilize test-meal residue as a criterion of gastric emptying it is essential that both the test-meal and the conditions of observation be standardized. The earliest efforts employed dietary test-meals like those of Riegel and Ewald; subsequently Sahli (117) proposed the admixture of a fat emulsion to the test-meal thus making possible a quantitative estimate of the extent of emptying after one hour. Particulate foods like rice, raisins and currants have similarly been employed in various labora-

torics. With subsequent refinement in the use of fluid test-meals, colored indicator substances also were added; at present all of these many procedures are being employed for this purpose.

How, from this diversity of procedures, can we pick out that which is most rational? As we see the problem it should be the function of a motility test to give a *quantitative* indication of the degree of gastric retention after a specified lapse of time, and preferably at repeated intervals following administration of a test-meal. This test substance should be as nearly physiological as possible—which a barium or bismuth meal is not. A mixed dietary meal, containing some non-digestible particulate matter, approaches this ideal—except that it does not lend itself to a series of determinations at short time intervals. Concerning the latter requirement, the fluid test-meal containing a suitable colored indicator is excellent though it may well be asked how representative it is from the digestive aspect. Also, if we adopt a fluid motor test-meal, the motility and secretory tests can be done simultaneously. It remains for the future to show which of these two types of motor meal is preferable. If the emptying time data obtained from both are closely analogous, the fluid meal should be adopted because it permits of simultaneous motor and secretory studies. If they are not analogous, it is still conceivable that we may want to adopt the fluid meal because it offers a standardized, though non-dietary, stimulus and a simple and inexpensive procedure. If it should be adopted, extreme care must be given to the choice of an indicator substance; this question will be discussed further on in the section on the estimation of volume of secretion.

B. Secretory response to psychic stimulation.

In the last decade of the nineteenth century Pavlov demonstrated beyond all question the existence of a psychic or cephalic phase of gastric secretion, as distinct from a chemical phase. If knowledge concerning the secretory activity of the stomach be accepted as important for clinical purposes, it is essential that we take cognizance of differences in pathological function which may exist between these two phases. This differentiation is all the more important in the light of our modern theories concerning the etiology of peptic ulcer, which place so much emphasis on the nervous or psychic factor. Therefore, the matter reduces to a search for an adequate criterion of psychic stimulatory activity as distinct from chemical stimulation.

As long ago as 1901, Schüle (122) studied the response of patients to coffee kept in the mouth for five minutes and then expectorated. In 1910, Curschmann (28) concluded that individual variations in response to a given test-meal might be ascribed to the fact that the test-meal proved unappetizing to the patient. To offset this, he offered the patient free choice of the meal to be used, and obtained results which he thought were significant, especially in cases of gastric neurosis. However, so far as the development of a specific psychic stimulus which will have universal applicability is concerned, the problem is probably insoluble. Hypnosis has been proposed, but it does not lend itself to routine application. The sight and odor of a tempting meal also offers obstacles in that the meal must vary with the previous conditioning of the individual and his response at any one time, even to the same meal, must be subject to numerous disturbing

psychological influences. Winkelstein, at our hospital, employs a procedure based on the chewing and expectoration of an orange—which seems to approach the desired end for a simple and direct psychic stimulus.

It may be, however, that instead of a direct stimulus of this kind, the best criterion of psychic secretory activity can be established without any specific stimulus at all, i.e., on the basis of the "continuous secretion." This would involve the periodic evacuation of the resting stomach by means of a duodenal tube; the obvious objection, based on possible mechanical stimulation of the mucosa by contact with the catheter, we now know to be invalid. The method has already been utilized by Galambos (46), Pollard and Bloomfield (108) and Schreiber (120). An excellent study on six normal young adults (female), extending over periods of one to six hours, has also been reported by Hellebrandt, Grant and Catherwood (57). The night secretion in response to a regular mixed meal, as utilized by Winkelstein (142) and others, does not satisfy the requirements of a pure psychic test and for this reason cannot find application in this connection. Of course, in applying a test based on the continuous secretion which is non-specifically stimulated, it is of the utmost importance that the patients' environmental conditions be properly maintained. But this, like a number of other factors, require further study and standardization before we can be sure that such a procedure can be used as a valid test of cephalic phase activity. We feel that the problem is of sufficient importance to merit the attention of clinical investigators in the very near future.

C. Secretory Response to Chemical Stimulation.

In contradistinction to the psychic phase of secretion there exist two chemical phases—the gastric, which is intermediated by gastrin from the antral mucosa, and the duodenal, which is effected by the intestinal absorption of secretagogues from foodstuffs. These two phases can easily be differentiated on experimental animals which have been provided surgically with antral and fundic pouches, intestinal fistulae, etc. With unoperated humans the problem of such a differentiation for purposes of clinical diagnosis is next to impossible. Hence we must treat the two as a single chemical phase, though should it ever become possible to study them separately we may find differences of great interest.

The transition from a gruel or Liebig's extract test-meal to one containing alcohol, caffeine, or other chemical substance reflects the need which has long been felt for a well-defined chemical stimulus. Because of the objections which had been raised to alcohol and caffeine, gastro-enterologists grasped at the opportunity which presented itself with the introduction of histamine into gastric physiology. Among the first to use histamine in gastric studies in humans were Cornot, Koskowsky and Libert (25); Matheson and Ammon (88); Gompertz and Vorhaus (51) and Andresen (1). Very naturally, many investigators contemplated the possibility of injecting this substance in place of using a chemical test-meal in fractional analysis. It soon became apparent, however, that histamine employed in this way could offer no distinct advantages over the usual test-meal substances (Dinkin and Wolff (33), Comfort and Osterberg (24), Gaither (45)); in fact, since histamine must be injected instead of being administered by mouth, the

acid secretory curve bears very little relation indeed to the stimulatory process arising within the stomach. On the other hand, in 1925, Gompertz and Vorhaus pointed out that a histamine injection might evoke a secretion of hydrochloric acid from individuals who gave no response whatever to the usual test-meals, and therefore it is an ideal agent for differentiating between true and false achlorhydria. Previously, in 1912, Ehrmann (36) had employed pilocarpine for this same purpose, but the violent secondary reactions from this drug made its general use impossible. Subsequently, the value of histamine in this respect was confirmed by others, e.g., Bockus and Bank (16), Dobson (34), Vandomfy (135) and Klump and Bowie (72); although Comfort and Osterberg (24) and Szmaz (132) stated that it possesses so few advantages over ordinary test-meals that its use may well be discontinued in favor of the latter (Eusterman and Balfour (39)).

It must be recognized that a chemical stimulus may be employed as a test for the responsiveness of either the glandular cells *per se*—by their direct stimulation—or of the nerve or other mechanism which ordinarily stimulates the gland cells. How alcohol and caffeine can be classified in this respect it is impossible to say at this time; histamine probably belongs to the former category. This same differentiation is implied in the clinical distinction between true and false achlorhydrias. Consequently, we believe that the histamine injection test cannot replace or be replaced by a simple chemical test-meal in a fractional series, but that they both yield information of decided value. In general, a single one-half or three-quarter hour specimen may be sufficient for the histamine test, since it is purely qualitative and acidity values have no diagnostic or physiological significance of any consequence.

We cannot leave the subject of histamine stimulation without giving some attention to dye excretion. Thirty or more years ago, Fuld (44) reported that neutral red is excreted by the gastric mucosa, following its intramuscular injection. In 1922, Finkelstein (42) showed that, of eight dyes so injected into dogs, only neutral red appeared in the stomach; that it entered through the canaliculi of the parietal cells was shown recently by Morrison, Gardner and Reeves (97). The following year Glacssner and Wittgenstein (50) reported that when the dye is injected into humans, the elimination of neutral red and the secretion of hydrochloric acid appear to run parallel, in that the time of first appearance of the dye is shorter than normal in cases of hypersecretion and longer than normal in hyposecretion; in cases of an acidity it does not appear at all. Therefore, the appearance time of the dye lends itself to a diagnostic test in the same way that histamine does.

This close parallelism could not be confirmed by Davidson, Wilcox and Haagensen (30); Winkelstein and Marcus (143); and Luria and Mogilevskii (83). Kartal (66) observed parallel behavior in only 70 per cent of the cases he studied. But, as Glaessner and Wittgenstein pointed out, these other authors employed an alcohol test-meal simultaneously with the neutral red injection, whereas they themselves studied the unstimulated stomach—hence the apparent difference in results. Since the human stomach is rarely in a complete resting state as regards hydrochloric acid secretion it would seem that the appearance time cannot be taken as a measure of secretory activity.

However, in a subsequent publication, Winkelstein and Marcus (144) reported the elimination of neutral red in all cases except the true achlorhydrias when a test-meal was given simultaneously with injection of the dyes and certain precautions recommended by Davidson (29) were taken. A similar conclusion had previously been arrived at by Davidson *et al* (30), namely, that the dye may make its appearance in the stomach even of patients with carcinoma and secondary anemia (though in small amounts), but never in cases of pernicious anemia. Its appearance in small quantities in these other instances, of course, may have been due to duodenal regurgitation, for Piersol, Bockus and Banks (106) have shown that the dye is excreted in the bile and duodenal secretion, as well as the gastric secretion of animals, and Cohen, Matzner and Gray (23) have been able to recover it from the stomach contents of pernicious anemia patients because of its excretion into the duodenum. We must conclude, therefore, that neutral red can serve no function not served by histamine, although it does not show the occasional toxic manifestations of histamine. Hence, until we know more about the physiology of neutral red excretion, we believe that it offers no signal advantage for either diagnostic or physiological purposes.

D. Volume of Secretion Versus Acidity of Gastric Contents.

In the early days of fractional analysis, abnormal cases were classified as hyper- or hypoacid. Subsequently, when physiologists had shown that the fluid secreted by the parietal cells probably always possesses approximately the same acidity, independently of pathological considerations, gastro-entcrologists realized that the variations in acidity which they observe in fractional curves are due to variations in the relative volumes of test-meal and parietal secretion as well as admixture of saliva and duodenal contents. From these considerations it follows that pathological variations in gastric secretory behavior, designated as hyper- or hyposecretory, should be evaluated in terms of the rate of secretion (i.e., the volume of secretion per time interval or per fractional specimen) rather than in terms of the acidity of the fraction.

Ordinarily it is impossible to determine the proportions of test-meal and gastric secretion in a fractional specimen, even if we assume that the volumes of saliva and intestinal fluid are negligible. However, if there be added to the original test-meal some non-absorbable substance in known concentration—some substance the concentration of which can be determined easily and with a fair degree of accuracy—the volume ratio of test-meal to gastric secretion can be calculated very easily, using the concentration of indicator substance in each of the several fractions and in the original test-meal. Such a substance we have designated elsewhere as a "dilution indicator."

The value of such a volume determination was realized well before the beginning of the present century, for in 1896, Mathieu (89) used an emulsion of oil in gum as a dilution indicator with a bread and tea test-meal. In 1910, Meunier (92) reported the use of kaolin and Laboulais and Goiffon (75) of sodium phosphate, and in 1919, Bausle (7) added $\text{Fe}_2(\text{SO}_4)_3$ to a test-meal for the same purpose. Unfortunately, all these efforts were abortive because these substances did not possess all the characteristics necessary for a reliable dilution indicator—non-absorption,

high solubility, non-reactivity with gastric contents, reliability of analytical determination, etc. Not until Gorham (52) introduced phenol red and Bloomfield and Keefer (13) introduced phenolphthalein were investigators in possession of reasonably satisfactory substances for the purpose. Although other substances have been proposed, e.g., Na_2SO_4 by Sary and Mahler (128) phenol red and phenolphthalein seem to be the only ones which have been extensively adopted by other workers. (Lewin (79), Gaither (45), Martini and Beck (87), Lanz (76), Bulger, *et al* (20) and Wilhelmj (139)). In our own laboratory we have investigated both these substances and have discovered that the use of phenolphthalein is completely invalidated by the fact that its solubility in stomach contents is much lower than its concentration in the original test-meal, and therefore most of the indicator

precipitates out within the gastric cavity (Penner, Hollander and Saltzman (103)). We are now using phenol red, for which we have developed a simple and reliable analytical procedure, in a systematic study of gastric analysis procedure to be reported on later (Hollander, Penner and Saltzman (60)). As yet, none of the results with dilution indicators reported on humans have been of significant value, for the several reasons stated above. It is questionable whether the dilution indicator method for evaluating volumes of pure secretion can ever be simplified sufficiently to be used as a routine clinical procedure. For research purposes, however, the technique contains many possibilities and the concept which underlies its use is of sufficient importance to merit its further investigation.

(To Be Continued)

A Disposable Non-breakable Hard Enema Tip*

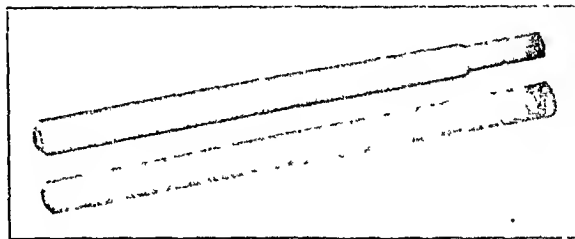
By

MANFRED KRAEMER, M.D., F.A.C.P.†
NEWARK, NEW JERSEY

SOFT rubber catheters, hard rubber and glass enema tips are in common use for administering enemas. These tips have certain common and individual disadvantages. They are all so expensive that they cannot be discarded after a single usage. They must be cleaned and sterilized each time they are used. While easy to sterilize, all are difficult to clean and even after frequent rinsings small bits of stool or barium adhere to their inner walls. The feces can be seen inside a glass tip and removed, but are often overlooked when opaque tips are used. Soft rubber tips are painful when introduced and in patients with fissures or other peri-anal lesions their introduction may be impossible. Rubber tips change in texture after several sterilizations. As manufactured, hard rubber tips are too short and the hand of the nurse becomes soiled with stool when she removes the tip from the tubing of the enema bag. For six years I have routinely used long glass tips for administering barium enemas. There is always the danger of breakage when these tips are inserted and in many hospitals their use is prohibited.

Through the co-operation of Mr. Herman Lerner of the Hygienic Tube and Container Company of Newark, I have had made a hard tip of a transparent, non-

inflammable plastic (cellulose acetate) simulating glass but unbreakable. These tips can be made so cheaply that they may be used once and discarded. I have substituted these tips for my glass ones and find them equally satisfactory. There is no fear of break-



age and subsequent trauma. Since the tips are used but once, the time consumed in cleaning and sterilizing is saved. The tips used are shown in the accompanying illustration. As the plastic is easily workable, tips can be manufactured to meet individual preferences. The tips cannot withstand boiling. If sterility is essential, they can be cleaned with soap and water and sterilized in alcohol, phenol or bichloride solutions.

Courtesy Miss Hazel Dearth, supervisor floor nurses at Presbyterian Hospital, tried the tips for routine enemas. They were time saving and economical as compared to soft rubber catheters usually employed

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An Attempt To Prevent Post-Operative Jejunal Ulcer By Aluminum Hydroxide Therapy*

An Experimental Study in Mann-Williamson Dogs

By

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WE have previously studied the effects of preparations of aluminum hydroxide on gastric secretion (1) by conducting controlled experiments in dogs. We observed no deleterious effects on the stomach or other organs. In view of these favorable results and the reports regarding the value of preparations of aluminum hydroxide in the therapy of "peptic ulcer" in man, it was deemed worth while to determine the effect of such preparations on the prevention of post-operative jejunal ulcer in Mann-Williamson dogs. It must be mentioned, however, that such a test of the value of any palliative remedy for "peptic" ulcer is a most rigorous one.

METHODS

Eighty-seven animals were operated according to the Mann-Williamson method except that an end-to-side instead of an end-to-end gastrojejunostomy was made. These 87 animals were divided into five groups for study. *Group I* consisted of 20 animals which were fed a limited amount of a special diet twice daily. This diet has been described previously (2). *Group II* consisted of 23 animals which given the same diet, and 10cc. of "Cremalin" hourly from xide cream (Cremaline) four times daily at 9 A. M. and at 1, 5 and 9 P. M. *Group III* consisted of 17 animals which were given the same diet and 10 grams of colloidal aluminum hydroxide powder (alucol) four times daily as in Group II. *Group IV* consisted of 13 animals which were given the same diet, and 10 cc. of "Cremalin" hourly from 8 A. M. to 8 P. M. and then at midnight. *Group V* consisted of 14 animals treated as those in Group IV except they received 3.2 grams of "Alucol" hourly and at midnight. Analysis of the acidity of the gastric contents was performed and the response to a test-meal was determined at frequent intervals.

RESULTS

Gastric Acidity. In Fig. 1 is shown the composite curves of the total and free acidity of the gastric contents in response to a test-meal before the operation and after the diagnosis of ulcer. The curves are based on an average of at least ten tests on each dog before and after operation. It is evident, as observed previously (3), that the acidity of the gastric contents of such dogs tends to be higher on the average than that of normal dogs.

In Fig. 2 is shown the effect of giving 20 cc. of "Cremalin" and of 10 grams of "Alucol" two hours after the ingestion of the test-meal. The curves represent composite results of five test-meals on each of five M-W. dogs. It is evident that the major neutrali-

zing and buffering effect of "Cremalin" is completed one hour after administration, whereas the effect of "Alucol" persists longer. This difference between the two preparations might be expected on the basis of the physical properties of the two preparations (1).

Prevention of Ulcer. The data pertaining to the prevention of ulcer are shown in Table I. The curves pertaining to the prophylactic value of the aluminum hydroxide preparations are shown in Fig. 3.

Aluminum hydroxide four times daily. It is to be noted that the average duration of life in the 20 controls, Group I, was 17.1 weeks; all died with ulcer

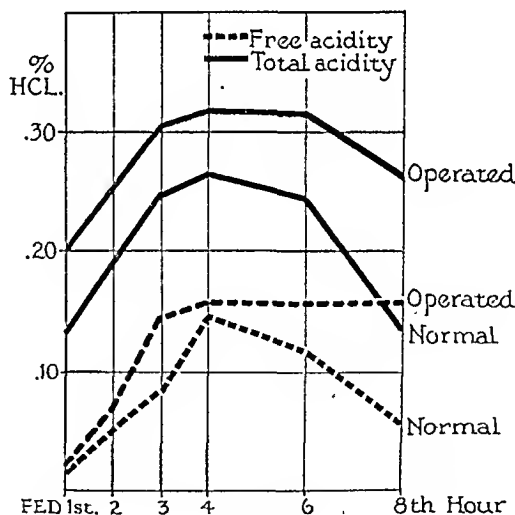


Fig. 1

except one (dog 20). The percentage survival time curve of this group of controls is represented by Curve A, Fig. 3. (It should be mentioned that the average survival time of 17.1 weeks is less than the 26 weeks previously reported for the special diet (2). This is due to the fact that in the previous study we gave the dogs all of the diet they would eat, whereas in this study the feedings were limited to 250 gm. twice daily because the aluminum therapy decreased appetite (vide infra). The M-W. dog does much better if he is given all the food he desires, because they suffer from intestinal indigestion).

When the aluminum preparations were given four times daily, the forty animals, Groups II and III,

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survived an average of 15.5 weeks, or 1.6 weeks less than the controls. Curves B and C in Fig. 3 are the percentage survival time curves for Groups II and III.

It is evident that the aluminum hydroxide preparations, given four times daily, were of no benefit. It cannot be said that they did harm because the difference of 1.6 weeks in survival time and 4 per cent difference in loss of weight (Table I) is too small to be of statistical significance.

Aluminum hydroxide hourly and at midnight. It is clear from the curves in Fig. 2 that the aluminum hydroxide preparations were neutralizing and buffering gastric acidity only for a relatively short period of time. The data in Table II further substantiate the two conclusions drawn above in regard to the effect of the M-W. operation on gastric acidity and to the failure of a single dose of aluminum hydroxide, although relatively large, to neutralize for a long period.

Since acid is a very important, if not a prime factor, in the cause of the ulcers being studied (3), and since

we were unable to detect any real injury to the dogs resulting from the aluminum preparations, we decided to give the Al hydroxide preparations hourly from 8 A. M. to 8 P. M. and then at midnight.

By preliminary tests we found that 10 cc. of "Cremalin" or 3.2 grams of "Alucol" hourly would prevent free acid from appearing in the gastric contents. The total daily dose of "Cremalin" was 130 cc.; of "Alucol," 41.6 grams. This dosage also controlled free acidity in the M-W. dogs during the day. No aspirations were made during the night, and there is no reason to think that free acidity was under control during the night, although the midnight medication was of benefit in that regard.

On referring to Table I, it will be noted that the animals receiving Al hydroxide preparations hourly (Groups IV and V) died with ulcer sooner than the animals receiving the preparations four times daily (Groups II and III) and also than the controls (Group I). On comparing curves A, E and D in Fig. 3, it be-

TABLE I

Group I		Group II		Group III		Group IV		Group V	
Controls Special Diet		Aluminum Hydroxide Cream 4 x Daily		Alucol 4 x Daily		Aluminum Hydroxide Cream Hourly		Alucol Hourly	
No.	Death with Ulcer— Week	No.	Death with Ulcer— Week	No.	Death with Ulcer— Week	No.	Death with Ulcer— Week	No.	Death with Ulcer— Week
1*	8	1*	8	1*	7	1*	7	1*	7
2	9	2	8	2	8	2	7	2	9
3	10	3	10	3	8	3	8	3	9
4	10	4	10	4	9	4	8	4	9
5	10	5	10	5	9	5	8	5	9
6	13	6	10	6	10	6	9	6	12
7	14	7	11	7	11	7	10	7	13
8	14	8	11	8	11	8	11	8	13
9	15	9	11	9	11	9	12	9	14
10	15	10	11	10	15	10	13	10	14
11	15	11	12	11	15	11	16	11	14
12	17	12	13	12	15	12	18	12	14
13	17	13	14	13	18	13	30	13	21
14	18	14	14	14	23			14	30
15	19	15	15	15	31				
16	20	16	16	16	10				
17	30	17	19	17	32**				
18	32	18	19						
19	40	19	20						
20	80**	20	22						
21		21	22						
22		22	34						
23		23	35						
Average	17.1		15.4		15.6		12.0		13.0
Ave. Body Wt. Loss	15%		20%		18%		30%		29%

*Publication number.

**No ulcer: was etherized.

Averages do not include those living 80 weeks or more without ulcer.

***Average for stock diet controls (Curve D, Fig. 3) was 11 weeks.

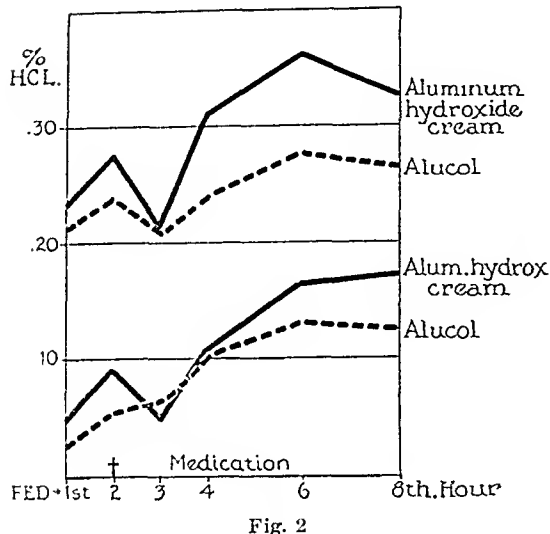


Fig. 2

comes evident that the hourly administration of the Al hydroxide preparations returned the "mortality curve" toward that of the animals on the stock diet shown by curve D. Obviously the more frequent administration of the aluminum hydroxide preparations was deleterious. It annulled to a large extent, the beneficial effects of the special diet, curve A, which is also reflected by the average losses of body-weight shown by the different groups in Table 1.

DISCUSSION

In view of the relatively great effort and expense involved, the results were *very* disappointing. The results raise a new question, particularly in view of the favorable results reported clinically. Why should aluminum hydroxide have the observed deleterious action in M-W. dogs?

A consideration of this question raises the matter of the etiology of the jejunal ulcer in M-W. dogs. At

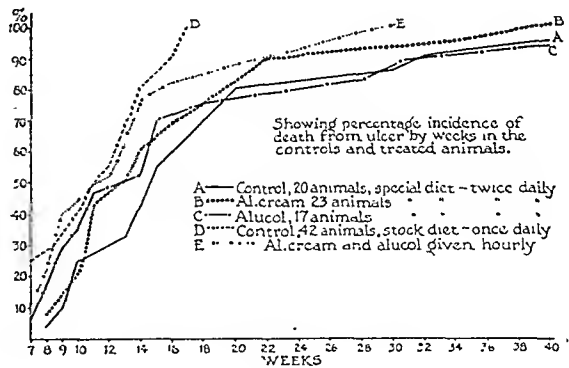


Fig. 3

least three etiological factors have been recognized, and we believe experimentally established. The first is acid irritation due to the absence of the alkaline bile and pancreatic juice. The second is the nutritional factor; these dogs have an experimentally produced intestinal indigestion; they lose considerable bile and pancreatic juice into the colon. The third is mucosal susceptibility; the jejunal mucosa is more sensitive to acid than is the duodenal. Attempts to control the acid factor in such dogs by the administration of alkalis have been of no (4, 5) or relatively little (8) benefit. Yet, when M-W. dogs are kept on a special diet and an extensive fundusectomy is performed, they do not develop ulcer (2). But, in this latter experiment the prophylactic therapy is directed both toward the acid and nutritional factors. This evidence would teach that the aluminum hydroxide therapy interferes with the nutritional factor, using the term nutritional in a broad sense. So, the question arises as to how aluminum hydroxide might disturb nutrition. The possibilities which occur to us are: (A) sufficient aluminum is absorbed to have a general toxic effect; (B) the aluminum interferes with digestion and absorption of organic food stuffs; (C) the aluminum inter-

TABLE II

	Preoperative Tests				Post-operative, Aluminum 4 Times Daily			
	Test-Meal 4 Hourly Aspirations Average		Aspirations, 4th Hour		Test-Meal 4 Hourly Aspirations Average		Aspirations, 4th Hour	
	Plain	Medicated	Plain	Medicated	Plain	Medicated	Plain	Medicated
	Free Acid	Free Acid	Free Acid	Free Acid	Free Acid	Free Acid	Free Acid	Free Acid
*Alucol Hydroxide Cream 15 Dogs Average	0.662	0.651	0.114	0.103	0.091	0.077	0.154	0.131
**Alucol 16 Dogs Average	0.651	0.644	0.110	0.103	0.109	0.084	0.165	0.129
Reference Column	I	II	III	IV	V	VI	VII	VIII

*Cremaline, 20 cc., 4 times daily.
**Alucol, 10 gm., 4 times daily.
No Alucol was given with the plain test-meals. Aspirations, 4th hour, means that the animal was fed the test-meal and an aspiration performed four hours later. In the regular test-meals, columns I, II, V, VI, an hourly sample was removed, the free acid values for each hour being averaged.

feres with the absorption or leads to excessive excretion of certain mineral food stuffs.

A. In regard to toxicity, we have in a previous study (1) failed to find that Al hydroxide is absorbed by normal dogs. But, in M-W. dogs, there being a deficiency of alkaline secretions in the upper intestine, the Al chloride entering the intestine from the stomach is reconverted into Al hydroxide more slowly than in normal animals. This would result in more irritation of the intestinal mucosa, and might remotely be conducive to absorption of Al. Unfortunately the tissues we took from our dogs for chemical analysis for Al, were exhausted before we were successful in making a satisfactory determination. In this regard we have subjected the various chemical methods for the determination of Al in tissues to a critical analysis and as a result lost faith in all the methods except the spectrographic method as employed by McCollum, Rusk and Becker (7). We could not try this method, because we did not have a suitable spectrograph available. With their method they found no Al in tissues such as liver, kidney and spleen, or less than 0.5 parts per million. In rats subsisting for 8 months on a diet containing as much as 0.6 per cent aluminum chloride, they failed to find aluminum in the liver, kidney and spleen. We doubt that Al was absorbed from the alimentary tract of our M-W. dogs.

B. In regard to the effect of Al hydroxide on the digestion of organic food-stuffs, we (6) have found that Al hydroxide does not cause an increase in the loss of fat and nitrogen in the feces of normal dogs. No evidence was obtained on this point in our M-W. dogs. However, *one fact was very evident in our M-W. dogs receiving Al hydroxide, and that was they lost more weight than the controls and they consumed less food.* Of course, irritation of the stomach and intestine decreases appetite via the vagi. And, we have previously submitted evidence (2) showing and emphasizing the importance of a large intake (3 to 6 lbs. daily) of a diet high in nuclear substances, vitamins and readily assimilable carbohydrates for the prevention of loss of weight and for definitely delaying the onset of ulcer in M-W. dogs.

Because of the effect of the Al hydroxide on the appetite of our animals and because we could not observe at autopsy any evident irritation of the intestine we searched further for a possible explanation of the cause of the anorexia. The explanation we believe resides in the effect of Al hydroxide on phosphorus or phosphate metabolism.

C. One of the findings of Taylor (8), who was a member of the Remsen Board to investigate the effect of Alum in foods, was that compounds of aluminum decrease the phosphates in the urine and increase correspondingly the phosphates in the feces. This effect would be of little consequence unless sufficient phosphorus, as Al phosphate, were diverted into the feces to induce a relative phosphorus deficiency. One

of the earliest and most conspicuous symptoms of phosphorus deficiency is lack of appetite which leads to a loss in weight. Also, phosphorus deficient animals use less digested protein for sparing body protein than control animals. These are the predominate results of phosphorus deficiency other than the changes in the bones (9, 10).

The foregoing explanation is the most obvious and only explanation we can find for the striking loss of appetite in our M-W. dogs and for the annulment of the beneficial effects of our special diet when Al hydroxide was administered. Whether this explanation is true awaits actual experimental demonstration. The requisite experiments are now under way.

Clinically the effect of Al hydroxide preparations on appetite has not been reported. Of course, it must be kept in mind that *we used large doses* in our experiments, because such doses were requisite for the continuous control of free acidity in our animals. It must also be kept in mind that we were dealing with animals suffering a relative pancreatic insufficiency. It would appear from our work, however, that Al hydroxide therapy would be contraindicated in a patient with a peptic ulcer associated with a relative pancreatic insufficiency.

SUMMARY

Two preparations of aluminum hydroxide (an aluminum hydroxide cream and colloidal aluminum hydroxide) were given to two groups of Mann-Williamson dogs on a special diet (87 dogs were used) to determine the prophylactic value against the jejunal ulcer that results post-operatively in such dogs. The first group received relatively large doses of the Al preparations four times daily. No prophylactic value was obtained. The second group received sufficient doses of the Al preparations at hourly intervals from 8 A. M. to 8 P. M. and another dose at midnight, to control free acidity continuously during the day. No prophylactic value was obtained. In fact, the therapy proved to be deleterious. The most striking effect of the Al was to cause a decrease in appetite, a decrease in dietary intake, and a more rapid loss of weight. The cause of this is discussed and the explanation is advanced, principally as an hypothesis for future experimental testing, that the aluminum, in the presence of a relative deficiency of pancreatic juice and bile for digestive activities which these Mann-Williamson dogs suffer, combined excessively with phosphates and produced a sufficient degree of phosphorus deficiency to reduce appetite. (The most conspicuous early symptom of a phosphorus deficiency is anorexia). These experimental results would indicate that aluminum hydroxide therapy should not be employed for treating a "peptic" ulcer complicated by the presence of a relative pancreatic and biliary insufficiency, as might occur with fibrous pancreatitis or a gastro-enterostomy.

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Chronic Localized Gastric Purpura*

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THE picture of the mucosa of the stomach in cases of hemorrhagic diathesis has been described similarly by all workers using the gastroscope (Schindler (24), Moutier (15), Gutzeit-Teitge (10), Henning (11)). If we gastroscopically examine a patient suffering from a purpura abdominalis Henoch, we find a pale noninflamed mucous membrane containing numerous hemorrhages of various size scattered throughout the mucosa. Emphasis has to be laid on the word "noninflamed." Inflammations of the gastric mucosa are extremely frequent, chronic nonspecific gastritis is the most frequent disease of the stomach, and its gastroscopic picture is characteristic. All easily recognizable changes are missed entirely in cases of generalized hemorrhagic diatheses. In them only noninflammatory hemorrhages are found, lying in the intact gastric mucosa as they are found to lie in the non-inflamed skin.

However, this picture is not characteristic of a general hemorrhagic diathesis. It also has been observed without a generalized tendency to bleed, merely as a *localized disease of the stomach*. This disease, and its typical development has been emphasized repeatedly (21). Later P. Chevallier and Moutier (5) made the same observation. They used the name: "Purpura chronique isolé de l'estomac." Although this expression may cause confusion because it may suggest some close relation with the well known disease of the skin which definitely does not exist, I am inclined to accept this name provisionally.

It seems to me that the "chronic isolated purpura of the stomach" is not only a new, but also an important disease. It has a definite gastroscopic and clinical picture. Gastroscopically, besides the already mentioned more or less numerous mucosal hemorrhages, dark brown round or star-shaped spots may be found. They are usually 2-5 mm. in diameter, but occasionally much larger. They apparently develop from the mucosal hemorrhages; the transition may be observed if the patient is gastroscopied at frequent intervals. Hemorrhages and pigment spots may be found along the anterior and posterior wall, but are most frequently in rows along the lesser curvature. The common site of their location is a point about 3 cms. above the angulus. The pigment spots disappear slowly, probably by absorption. However, some hemorrhages, instead of being absorbed, become ulcerated and develop into a hemorrhagic erosion, red, grayish-red or brownish-red in color. Gastroscopy has verified the observation of older pathologists: that true hemorrhagic erosions do exist. By the fact that they may become ulcerated, the eruptions of the localized purpura of the stomach are definitely different from the skin-eruptions in generalized purpura. However, it is easy to explain this difference. In the stomach the acid gastric juice developing peptic power is present;

it is more than likely that the gastric wall may lose its autoprotective power against autodigestion if it is damaged over a too long period of time by some disturbance of the circulation. The frequent coincidence of such isolated gastric purpura with true gastro-duodenal ulcer does not prove that hemorrhagic erosion is the acute stage of chronic gastro-duodenal ulcer. Chronic inflammation also often is observed in stomachs containing true gastro-duodenal ulcer, and nevertheless I believe that the inflammation is secondary to the ulcer. However, it would not be easy to explain the presence of noninflammatory gastric hemorrhages by assuming that they are effected by the ulcer; it would be very difficult to explain why they so often are found at the place of predilection of ulcers, namely at the angulus; and finally, I believe I have observed the transition of mucosal gastric hemorrhages into true gastric ulcer.

Therefore, I believe that—

1. there is a definite relationship between chronic localized gastric purpura and chronic gastro-duodenal ulcer,—that
2. chronic isolated gastric purpura may precede or follow chronic gastro-duodenal ulcer or they may be found together,—and that
3. the hemorrhagic erosion, having its origin from the chronic isolated gastric purpura by the peptic quality of the gastric contents, may be the acute stage of chronic gastro-duodenal ulcer.

CASE HISTORIES

Some abbreviated case histories may give an idea of the clinical picture of chronic isolated gastric purpura and its consequences.

(a) Mucosal hemorrhages in normal mucosa.

Case 1. A girl, twenty years of age, had suffered from epigastric distress for three years. The pain was of the ulcer type, delayed, periodic. Gastric analysis revealed free acidity of 56, total acidity of 75. Free HCl also was found in the fasting stomach. No occult blood was found in the feces. Repeated X-ray examinations failed to reveal any abnormality. Since most refined repeated examinations did not discover any disease she was treated for years as a psychoneurotic. Finally gastroscopy revealed two marked hemorrhagic spots above the angulus in the lesser curvature, i. e. at the common ulcer site. After a period of careful ulcer management the distress disappeared completely, and at the time of the last report several years later it had not returned.

(b) Mucosal hemorrhages, pigment spots and hemorrhagic erosions in a case of severe gross hemorrhages.

Case 2. A white woman, fifty-six years of age, had had several gross hemorrhages during the past years. X-ray examination with the compression technic did not reveal any evidence of gastric disease; at gastroscopy the entire stomach was well seen; the activity of the pylorus was normal. In the greater curvature of the antrum there were two round pigment spots. In the lower part of the body almost all the folds contained mucosal hemorrhages and pigment spots, without any sign of inflammation. In

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the anterior wall two definite superficial erosions were seen, surrounded by a hemorrhagic area; one of the erosions was yellowish-gray in color, the other brilliant white. Below the cardia extensive hemorrhagic areas were observed without inflammation. The mucosa appeared pale. The gastroscopic impression was:

1. numerous mucosal hemorrhages of various sizes
2. multiple pigment spots
3. two hemorrhagic erosions.

Two days later the patient had again a severe but not fatal gross hemorrhage.

Hemorrhagic noninflammatory erosions as the source of gross gastric hemorrhages are not very rare. I have observed three such cases.

- (c) Hemorrhages, pigment spots and gastric ulcer.

Case 3. A thirty-three year old female complained of epigastric distress. The physical examination was negative. The Ewald test of gastric secretion disclosed a free acidity of 52, a total of 70. The benzidine test of occult blood in the stools was negative. An X-ray examination of the stomach was negative. Gastroscopy: The lesser curvature was covered with star-like and streak-like small pigment figures; in some places, especially in the posterior wall there were fresh mucosal hemorrhages. In the anterior wall, below a fold in which three pigment spots were seen, there was a round ulcer with quite a sharp edge about 1½ cm. in diameter, its floor yellowish, its edge toward the pylorus, pigmented, toward the cardia, hemorrhagic. Otherwise the mucous membrane was normal. This ulcer had apparently developed in a hemorrhage which already had partly changed into pigment.

- (d) Mucosal hemorrhages and duodenal ulcer.

Case 4. A forty-three year old female had complained of epigastric distress of the ulcer type for eight years. Gastric analysis revealed a free acidity of 20 and a total of 52. X-ray disclosed a frank deformity of the duodenum, typical of duodenal ulcer. At gastroscopy no gastric changes were noted, except that there were many discrete and linear-shaped mucosal hemorrhages and pigment spots on a fold of the lesser curvature.

- (e) Mucosal hemorrhages after ulcer.

Case 5. A thirty-two year old female complained of pain in the epigastrium, belching, and heart-burn. X-ray examination disclosed a duodenal ulcer with a moderate stenosis. Operation (Dr. Dragstedt): small puckered scar on the anterior wall of the duodenum. Incision was made through the pylorus and extended into the duodenum and stomach. An ulcer about 1½ cm. in diameter was found on the posterior wall of the duodenum. A pyloroplasty was performed. Four years later the symptoms recurred. Gastroscopy on May 2, 1935, showed a gastric ulcer without inflammation. Ulcer management was resumed. Gastroscopy on July 16, 1935: the site of the ulcer previously seen was somewhat elevated and scar-like. On the lesser curvature just above the angulus were many small mucosal hemorrhages. Similar hemorrhages were present on the lowest part of the posterior wall.

The incidence of localized gastric purpura after the healing of gastric ulcer is so frequent that numerous respective case histories could be quoted.

- (f) Hemorrhagic erosion after ulcer.

Case 6. A forty-five year old male complained of abdominal pain and vomiting of two months' duration. The pain was left-sided, not related to food. Slight tenderness was present in the epigastrium. X-ray reported an enormous dissecting ulcer on the lesser curvature of the stomach. Gastric analysis revealed a free acidity of 72. The benzidine test for occult blood in the stool was strongly positive. Six months later X-ray reported complete healing of the ulcer. Gastroscopic examination reported the action of the pylorus to be normal. No ulcer or scar was found anywhere along the lesser curvature. Near the lesser curvature above the angulus in the anterior wall there were some hemorrhages, in one of which

was seen a flat but definite erosion with an extremely red edge. All other parts of the stomach were quite normal. Diagnosis: Typical hemorrhagic erosion. The patient at this time was feeling fine. One year later gastroscopy reported the following: At the point where the smooth musculus sphincter antri touched the lesser curvature there were mucosal hemorrhages. Other streaky and spotty hemorrhages were seen in the mucosa of the lesser curvature and the posterior wall. A single small hemorrhage was seen on the greater curvature. The hemorrhagic erosion had healed. Diagnosis: Healed hemorrhagic erosion. Numerous hemorrhages were in the normal mucosal membrane.

It thus becomes evident that, although hemorrhagic erosions and even large ulcers may heal, the stomach still retains the characteristics which I interpret as those of the "ulcer" stomach, namely it presents the picture of a localized gastric purpura.

- (g) Bleeding hemorrhagic erosion, hemorrhages, pigment spots and duodenal ulcer.

Case 7. A forty-five year old male complained of gnawing epigastric pains one-half to two hours after meals. A physical examination was negative. The benzidine test revealed a trace of occult blood in the stools. The histamine test of gastric secretion revealed a free acidity of 32. Roentgenologically a deformity of the duodenal bulb characteristic of duodenal ulcer was reported. Gastroscopy reported the whole stomach to be seen. The pylorus was round and widely open without contraction. The anterior wall of the upper region contained many large hemorrhages, pigment spots, and in some places small, hemorrhagic erosions. One of the latter was freshly bleeding into the cavity of the stomach. Radial folds were converging toward this point. The aspect of the contiguous mucous membrane was normal.

In this case the bleeding of a hemorrhagic erosion was actually seen.

DISCUSSION

These case histories show that chronic localized gastric purpura often presents clinically the picture of an ulcer though no ulcer is present. The mucosal hemorrhages are transformed into pigment spots, then absorbed. Sometimes hemorrhagic erosions develop in them, eventually severe gross hemorrhages may occur. The formation of true chronic ulcer from these acute hemorrhagic erosions is likely. Chronic localized gastric purpura is often found together with a chronic gastric or duodenal ulcer, or may be found before the development of such an ulcer or after its healing in 44 per cent of all cases observed. Not infrequently chronic localized purpura is observed over a long period of time without an ulcer developing. This uncomplicated chronic localized gastric purpura is observed in 5.6 per cent of all patients examined gastroscopically.

PATHOGENESIS

The question of the pathogenesis of this almost unknown disease leads to the most interesting statements. Almost all research work done on the great problem of the hemorrhagic diatheses has considered exclusively blood and blood vessels. The American school in the beginning had different conceptions to be mentioned later, but finally the influence of the German school prevailed, and more or less the conceptions of Frank (7), Glanzmann (8), etc., were adopted. Glanzmann subdivided purpura in the two great groups of anaphylactoid and thrombopenic purpura, but already Morawitz (14) recognized that reduction in the number of the thrombocytes is a subordinate finding.

It is not possible to consider general disturbances to be the cause of *localized* gastric purpura. If the blood were diseased, why should such a blood disease cause extravasations only in the area of the stomach, or why should the vessel walls be altered only in this area? This is not yet understood. Therefore, the observation of chronic localized gastric purpura leads us back to older opinions of American authors who believe that the *nervous system* has the decisive role in producing hemorrhagic diatheses. Probably the first man to advance this opinion was *Weir Mitchell* (13). He wrote on "Purpura as a neurosis." He described neuralgias accompanied by muscular spasms in which at the place of the most outspoken pain regularly ecchymoses developed. He observed furthermore cases of purpura in which accompanying pains and symmetrical distribution of the eruptions led him to the diagnosis of a neurosis. He asked whether certain conditions of the nervous system would be able to weaken the walls of the blood vessels so that they become permeable for the red blood cells. Better proofs for the primary affection of the nervous system in hemorrhagic diatheses were presented by *Castex* (3, 1) anatomically, and by *Schindler* (22) clinically.

Castex was the first (the paper of *Gordon* (9) is not convincing) to demonstrate definite histological changes of the central nervous system in two cases of symmetrical purpura. He found severe changes of the cells of both lateral superior nuclei of the sympathicus, reduction of the number of cells, diminution of the still existing cells, retraction of the cell body, central chromatolysis with accumulation of the granulations at the periphery, diminution of the number of the dendrites, briefly all those changes which are found in cell sclerosis.

These findings concerned the spinal centre. *Schindler*, however, believed that purpura-eruptions may occur if any part of the vasomotor tract is diseased. He observed noninflammatory purpuric skin eruptions in neuritis, tabes, combined cord degeneration, multiple sclerosis, lethargic encephalitis, hemiplegia, and in one case of brain tumor in the skin only of the paralytic extremity.

Is destruction or alteration of the nervous centres known in cases of localized hemorrhages of the gastric mucosa? Experimental research has provided us with ample material to prove that lesions of the hypothalamus may cause hemorrhages of the gastric mucosa and superficial hemorrhagic erosions.

The first research in this subject was carried out by *Schiff* (19) as soon as 1867. *Brown-Sequard* (1) in 1876 wrote on alterations of the gastric mucosa following cerebral lesions. However, a new interest in this connection arose following the *Balfour* lecture of *Cushing* (6) in 1932 who believed in a connection between hypothalamic disturbance and certain gastro-intestinal lesions. *Burdenko* and *Mojilnitski* (2) produced small lesions in the base of the brain which resulted in gastric hemorrhages and erosions, acute ulceration and occasionally perforation with peritonitis. They assumed destruction of a vasomotor centre in the posterior hypothalamus and of a metabolic centre in the tubular region. *Watts* and *Fulton* (25) worked on the effect of lesions of the hypothalamus upon the gastro-intestinal tract and heart in monkeys.

Multiple erosions of the stomach were encountered after hypothalamic injury. They occurred most frequently in the body of the stomach. Of seventeen animals with large hypothalamic lesions, four developed gastric erosions, one died of a *perforated duodenal ulcer* and frequently mucosal hemorrhages were found. In the control series erosions were found only in one monkey who had had a midthoracic resection of the spinal cord. Other spinal or cerebral lesions did not lead to erosions. *Hoff* and *Sheehan* (12) also experimented on monkeys. Following hypothalamic injury five animals of sixteen showed *multiple hemorrhagic erosions* in the mucosa of the body of the stomach.

With these experiments a definite connection between lesions of the hypothalamus and the development of mucosal gastric hemorrhages and hemorrhagic erosions of the stomach is established. Some connection between such lesions, gastric mucosal hemorrhages and erosions, i. e. chronic isolated gastric purpura, and true gastric ulcer seems to be likely at least.

How is it possible to explain extravasation of blood following lesion of the vasomotor tract, resp. of the hypothalamus? The theory of spontaneous hemorrhages has been advanced decisively by *Natus* (17). He experimented on the duodenal coil and the pancreas of rabbits and came to the conclusion that protracted irritation of the vasomotor nerves leads to complete interruption of the relation between nervous system and wall of the blood vessel. He found that the irritability of the vasodilators disappeared and finally stasis occurred, although the activity of the heart was not impaired. When this stasis developed slowly *extravasation of red blood cells* from the capillaries was seen. The blood stasis in a portion of the capillaries caused resistance resulting in increased side-pressure in the neighboring still working capillaries, and this increased side-pressure expressed the blood into the tissue. Therefore it may be assumed that lesion of the vasomotor tracts of the gastric nerves leads to stasis in the capillaries and subsequent mucosal hemorrhages. It is possible that vagus stimulation leads to continuous production of acetylcholine, and that this production of acetylcholine causes diminished blood flow through the stomach, as described by *Necheles* (18), with stasis and extravasation of blood. Therefore it is easy to understand that lesions of the hypothalamus may lead to gastric purpura. The gastric peptic juice then may erode the weakened gastric wall causing hemorrhagic erosions. And it is easy to understand that, if the nervous irritation lasts too long, chronic ulcer can develop.

CONCLUSIONS

1. The clinical and gastroscopic picture of chronic isolated gastric purpura is described and illustrated by case histories. Its relation to mucosal pigment spots, gastric hemorrhagic erosions, and chronic gastro-duodenal ulcer is discussed.

2. An attempt is made to explain the pathogenesis of this disease—according to *Castex*'s conception—by assuming lesions of the nervous system. The mechanism of lesions of the vasomotor tract leading to spontaneous blood extravasation is described.

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A Review of Some Foreign Literature

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1. GERMAN

ASCHOFF (1) published a series of articles on the anatomy of senility. These short but exhaustive descriptions may become classic. Here the article on the "digestive tract in senility" is of special interest. The expression "senility" refers to the ninth and tenth decade of human life. Because of the loss of elastic tissue the entire alimentary tract becomes longer in senility. The mouth presents loss of the teeth, atrophy of the jaw, prominence of the chin. (The order in the loss of teeth is a definite one, the premolars being the first, the canini the last to be lost. In the tonsils regressive processes are observed; true angina is very rare in senility). The tongue shows senile atrophy of the voluntary musculature, the mucosa is thinned, but patchy leukoplakias are also found. However, carcinoma of the lip may be found without preceding leukoplakia. It is found only in men and probably is due to irritation by the tar-containing juice of pipes. In the esophagus leukoplakia is found. The lower end of the esophagus becomes more movable than it was before, and that may lead to the formation of hiatus hernia. The stomach shows often a marked thinning of the mucosa, the system of folds disappears, the glands of the corpus are replaced by pyloric duodenal glands. This happens especially along the "Magenstrasse."

Slowly the area of the acid secreting mucosa is diminished. This may be a reason why in senility fresh ulcerative lesions are rare. Ulcer-Cancer is not characteristic in old age, but other forms of cancer occur in the atrophic gastric mucosa, produced by the attempts of the epithelium to regenerate. The shape and position of the stomach are changed, a horizontal position being frequent. The intestine becomes more and more immune to bacterial attacks. Typhoid and dysentery are almost unknown in old age. Carcinoma is more frequent in old age than in senility. Appendicitis is very rare, but diverticulosis and diverticulitis are frequent. The salivary glands show atrophy. Their

cylindrical epithelium changes into squamous epithelium. Therefore, staphylococci infections are frequent. Cirrhosis of the pancreas is not a disease of senility. Its fat hypertrophies to replace the glandular tissue. The number of oncocytes (special cells stained yellow with Sudan III) increases. The chief disease of the liver in senility is not cirrhosis but brown atrophy. The lobules are diminished in number, brown, their centres being reddened. Microscopically accumulation of lipofuscin is seen in the small liver cells. No senile changes of the biliary ducts occur.

The relation of *vitamines* to diseases of the alimentary tract is now of much interest. Einhauser (2) believes that hypovitaminic conditions are more frequent than avitaminoses. In cases of C-vitamine-deficiency, inflammation of the alimentary tract is frequent. He quotes Eusterman's opinion on the importance of Vitamins C in the healing process of gastric ulcer and Thiele's observation that gastric hemorrhages are frequent especially when a scarcity of Vitamins C-containing food exists. Vitamin C-deficiency may be caused by insufficient absorption in the gastro-intestinal tract. Patients with anacidity did show increase of the reduction-value in the urine when ascorbic acid was injected, but failed to show this phenomenon when the ascorbic acid was given by mouth. However, when the ascorbic acid was given in an "acid milieu" by adding lemon juice, sufficient absorption took place.

The discovery of the frequency and importance of chronic nonspecific gastritis has brought out a great many questions, especially as far as definition and classification are concerned. Every paper from Katsch's clinic has to be considered carefully because Katsch was one of the first men to discuss and advance these complex problems (see his chapter on Chronic gastritis in Bergmann-Staehelin, *Handbuch der inneren Medizin*, Berlin, 1926 Springer, III. Bd. 1. Teil, p. 554). He has recently described two new types of gastritis: the mucoid and the serous gastritis. Now, Baltzer (3) undertakes to describe the methods of

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recognition and to discuss their value in diagnosis. He claims that always three different adjectives should be added to the diagnosis of gastritis: the first indicating the clinical picture, the second indicating the function, and the third one indicating the specific anatomic lesion, as for instance: "Gastritis acuta dolorosa, superacida mucosa, polyposa of the body." Such a concept cannot be easily accepted. The re-introduction of the diagnosis "gastritis" presupposes our knowledge that definite anatomic inflammatory changes of the stomach exist, and that compared with these anatomic pictures clinical symptoms as well as function are relatively meaningless. This consequence will be drawn easily from the extensive and critical research work of Baltzer himself. He emphasized that in cases with increased mucus of the gastric juice usually no gastric disease is found, but that an "instability of the whole organism" exists. There is no objection to add adjectives denoting one or several partial functions to the anatomic diagnosis of gastritis, but first one must know whether or not there is an anatomic substrate for subjective symptoms and alterations of function. The paper of Baltzer describes the methods of measuring albumin and mucus in the gastric contents, and gives a clinical survey.

The papers read at the Second International Congress of Gastro-Enterology in 1937 (4) have now been published and many of the papers are of interest. The discussion on the early diagnosis of gastric carcinoma brought out important contributions. Kapp's statistics are of special interest (p. 592). Gastric distress was found to have been present for 7.3 years in the average of 39 cases of carcinoma of the corpus, for 2.4 years in 66 cases of pyloric carcinoma and for 0.33 years in 15 cases of carcinoma of the cardia. Sometimes the story was brief, in other instances long, up to 30 years. In a large group of cases indefinite symptoms such as epigastric pressure, fullness, weakness, belching, lack of appetite were present for a long time and usually were considered to be the symptoms of a psychoneurosis. Gastroscopists know that these symptoms are very suggestive of chronic atrophic gastritis. Therefore, one group of gastric carcinoma probably develops from atrophic gastritis. This has been proved also by histologic examinations. According to the histories in 12 of 66 cases of pyloric carcinoma and in 24 of 39 cases of body carcinoma gastritis probably preceded the development of the carcinoma.

Therefore Kapp also checked over 157 cases of gastritis observed at the Basel University Clinic. Five years or more later 21 of these cases or 13.4% were treated because of gastric cancer. The average time elapsed between the making of the diagnosis of chronic gastritis and the finding of a carcinoma 12.5 years. Similar observations were made by Uslan who, in 125 cases of gastritis, found that gastric carcinoma developed in eighteen. In one-seventh to one-eighth of

all patients suffering from chronic gastritis, gastric carcinoma develops. Kapp believes that we need periodic checks of all patients suffering from chronic gastritis in order to come to an early diagnosis of gastric carcinoma. This opinion is shared by Katsch (p. 372) who claims that much of the money and effort spent on cancer research should be used in research on chronic gastritis.

2. THE DUTCH LITERATURE

It is interesting that a book on gastroscopy has now been written in the Dutch language. Bloem's (5) monograph though based on a limited number of personal observations, is very satisfactory. Of special value is his thorough knowledge of the literature and his exhaustive description of the development of gastroscopy.

3. THE FRENCH LITERATURE

The relation between diseases of the stomach and the blood will be the chief topic of the next international gastro-enterologic congress. An exhaustive study has been made by P. Chevallier and Fr. Moutier (6). The mucosal changes occurring in pernicious anemia, chlorosis, secondary anemias of different kind, and in purpuras have been observed gastroscopically in numerous cases. Four colored plates show the generalized atrophies, the "nacreous patches" found in pernicious anemia, and the noninflammatory hemorrhagic phenomena of the gastric mucosa (localized autonomous gastric purpura). Moutier and Debray (7) describe the pathology of the "juxta-pyloric" region of the stomach. Congenital diverticula, spasms, ulcers, tumors of this region are described and pictured.

Moutier (8) contends that the stomach resembles the skin in that there are some definite types of inflammation, but besides them a great number atypical lesions which do not belong to any definite type and haven't any definite symptomatology. He describes the "Gastrite boutonneuse" (pustular gastritis) as belonging to this group. He observed in five patients pustular, whitish, stump-like lesions, seen together with some type of gastritis, but disappearing after a short time. Although the presence of these lesions cannot be denied it remains questionable whether it is wise to give them a name of their own. Evidently they may be seen in edematous, atrophic and other forms of gastritis. However, the observation is a very interesting one. In Beaumont's classical description of gastritis changes occurring in Alexis St. Martin's stomach, there was only one lesion which 100 years later was not seen at gastroscopy, namely that of vesicles. Moutier's observation of whitish pustules recalls to our mind Beaumont's description of vesicles. Perhaps Beaumont has been correct even in this last point.

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Problems of Maintaining Nutrition in the Highly Food-Sensitive Person*

By

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DURING the last few years medicine has been passing through a stage in which any one of us physicians does well if, in a given case, he suspects that the symptoms complained of are due to marked food-sensitiveness, if he succeeds in identifying the offending foods, and if by removing them from the diet he works a cure. These are no mean accomplishments, but the time has come when we must not rest satisfied with them but must demand of ourselves another, namely, that of replacing the hurtful foods taken away with enough harmless ones so that the patient can remain well nourished and contented. Unfortunately, as yet, most of us seem to be mainly concerned with the *taking away* of foods, and as a result, we are beginning to see a certain number of emaciated men and women whose plight is due to too long an adherence to some highly restricted and inadequate type of diet.

MAINTAINING NUTRITION IS SOMETIMES DIFFICULT

Sometimes one cannot blame anyone for this situation because the problem of maintaining good nutrition in an adult or child who begins to wheeze or sneeze or bloat within a few hours after eating even small amounts of such commonly used and important foods as wheat, milk, eggs and beef, must obviously be difficult. I have under my care a woman who, when I first saw her, could live in comfort on only two foods. At first almost every effort I made to find something new for her resulted in a bad digestive upset with pain, diarrhea, loss of sleep, and loss of weight, and only after much searching did I find a number of foods that she could eat with comfort. Curiously, when these were found, all sorts of bizarre symptoms left; she began to gain in weight, and her bowels moved normally.

THE NEED FOR TAKING FOODS IN ROTATION

Naturally, unfortunate people like this must soon become bored with their narrow diet. Also because they eat so much of the few foods that they can take and eat them so often, they are likely soon to be sensitized to them, and thrown back onto starvation rations.

Some time ago a patient like this, who was almost at the end of her rope and facing starvation, solved the problem by taking in rotation the foods to which she was only slightly sensitive. As all allergists know, there are many persons who can take a small amount of a harmful food at intervals without serious trouble, but if they are to eat larger amounts or particularly if they eat the food every day for several days, they get into serious trouble. The trick then is to eat each mildly harmful food once a week or so, so that its effects will not become cumulative.

The trouble is not in their heads. Some physicians

and dietitians suspect that in these cases the trouble is "in the patient's head," but it isn't. It is in some fussy persons with many prejudices and dislikes, but an expert can soon distinguish these persons by their behavior and their answers to searching questions.

One of the most useful features about an elimination diet is that it exposes the overly fussy, the psychopathic, the unreasonable and the stupid patient within twenty-four hours, and shows how hopeless it is in the particular case ever to fit *any* diet that will work.

One of the best proofs that the troubles of a patient are not due to imagination but to specific food-sensitiveness is that he gets sick when the offending food was so well concealed in some harmless looking dish that he had no suspicion that he ate it. Thus, a friend of mine who is highly sensitive to oysters, almost lost his life one night through eating a few mouthfuls of duck which he would never have touched if he had suspected that the dressing contained a few chopped oysters. Within a few minutes after eating the duck, the man was lying on the floor, unable to breathe, black in the face, and almost unconscious. He had forewarned his host of his idiosyncrasy, but the cook had no patience with "such foolishness" and in went the oysters anyway.

Another of my friends dreads dining out because of his great sensitiveness to cottonseed oil. He thought he had learned to avoid all foods that might possibly contain this oil, but recently he came to grief in a curious way. When, after a quiet dinner at home, the typical retching started, the only food that could possibly be looked on with any suspicion was some dates; but how could these have come in contact with cottonseed oil? The mystery was solved next day when the grocer explained that since people like their dates shiny, he wipes off the top ones in the box with an oil-soaked cloth!

Another patient who is highly sensitive to chicken will, in spite of every care, occasionally fall ill with the syndrome which he knows all too well. Inquiry then reveals the fact that an innocent looking cream soup eaten four hours before happened to have been made with chicken broth instead of beef stock.

The need for the proper labeling of foods. I might go on telling many interesting stories of this type, all showing, first, that these allergic people are not imagining their troubles, and second, that it is highly desirable that they be given information as to the composition of the foods that are set before them or that they buy from the grocer. Obviously, it would be helpful to them if the purveyors of foods would list on the label all of the materials that go into a particular can or bottle or package.

Here, for instance, is a woman to whom any trace of a corn product is poison. How can she know as she eats some canned fruit, jelly, candy, mayonnaise, "olive oil," sardines, or bakery product that she is not

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going to ingest some corn sugar, corn oil, or corn starch? Here, too, is the mother of an asthmatic child who wheezes and snuffles all night if a little wheat, milk, or egg gets into his food. When she buys him some arrowroot cookies how can she tell if there is any trace of the offending foods in them?

"Arrowroot" may be many things. But even if she could find this information on the label this might not solve her problem. It is conceivable that the child might be insensitive to the common "arrowroot" made from the West Indian Maranta, but sensitive to the Tous-les-mois or Queensland variety made from a species of Canna, or to the East Indian arrowroot made from a species of Cureuma, or to the Brazilian arrowroot made from cassava, or to the Tacca arrowroot made from the pia plant of Tahiti, or to the Portland arrowroot made from an Arum. A child highly sensitive to potato would be made ill also whenever the food manufacturer let himself be cheated into buying arrowroot highly adulterated with cheap potato starch.

This paragraph on arrowroot alone should show what a difficult situation the allergic person is now up against when he tries to avoid eating one or more foods to which he is highly sensitive.

The Food and Drug Act does not help. I understand that the Food and Drug Administration has urged Congress to help markedly allergic persons by revising the law so as to require manufacturers to list on their labels the several constituents of foods, but the proposal has been fought by men who fear either to give away trade secrets or to run up against certain prejudices of housewives.

Food packers may help voluntarily. It may be that some day such labeling will be compulsory, but what I think will happen first is that some of the packers will find that it pays to cater to the needs of the group of highly food-sensitive persons, just as it pays now to supply mothers of delicate children with finely puréed and comminuted vegetables of all kinds, and I presume it pays to supply diabetics with special breadstuffs and fruits which are canned without syrup.

Especially if the allergists of the country were to help in disseminating information about the properly labeled foods, a good business might soon be developed. A hopeful point for the manufacturer would be that the potential market seems constantly to be increasing. Either we physicians are coming to recognize allergic troubles more often or else the percentage of allergically sensitive persons in the community must be increasing rapidly.

It is hard to estimate the number of highly food-sensitive persons in this country, but one can get some idea of how many there are among persons with indigestion. When Hinshaw and I questioned 500 patients we found almost everyone had to avoid one or two foods. Twenty-six per cent were sensitive in some degree to milk, 18 per cent were sensitive to chocolate, and 13 per cent were sensitive to eggs. But when we made a list of the persons made *severely ill* by eating foods we found 7 per cent (of the 500) sensitive to milk, 5 per cent sensitive to chocolate, 4 per cent to apples, 3 per cent each to eggs and tomatoes, and 2 per cent each to cabbage, meat, corn, coffee and bananas.

Vaughan, in his survey of 500 villagers in Virginia, and Hughes, in her study of 1,000 avowedly healthy persons, each found about 60 per cent who were food-

sensitive. Rowe found 31 per cent food-sensitive among 400 university students and nurses. The percentage arrived at in any such canvass will depend on the care and pertinacity used in the questioning.

The need for special bakeries. Already Rowe has found it necessary to get a baker to supply some of his allergic patients with wheat-free breadstuffs made of only one or two starches obtained from such sources as rice, rye, potato, barley and the soy bean, and doubtless more such bakeries will some day be opened.

THE USE OF FOODS NOT ORDINARILY USED IN AMERICA

Allergists will doubtless soon be reaching out to the ends of the earth to secure new foods which, if our original theories were correct, should never cause the American patient trouble because he has never eaten them and therefore has not had an opportunity to become sensitized to them. Although this securing of new foods is helpful, it does not solve all our problems because there are some persons so sensitive as to react violently to many a food which, so far as can be determined, is new in their experience.

According to Vaughan, the reason for this is found sometimes in the close botanic or biologic relationship of the new food to some old one to which the person is sensitive. Thus a man who is sensitive to orange juice is likely to be sensitive to grapefruit juice, but he doesn't have to be. Sometimes the sensitiveness is specific, as in one of my friends who is highly sensitive to chicken, domestic duck and goose, but not to turkey, pheasant, guinea hen, squab or wild duck.

Although, then, a new food never eaten before may prove injurious to a highly allergic person, the physician can sometimes work a miracle for some poor half-starved person by reaching out to Asia or Africa for new articles of diet. Thus, one of my patients, who had starved down to 89 pounds, was given a new lease of life when in some food stores patronized by immigrants she found such foods as dried Lichi nuts and chestnut flour from China, garbanzos and favas from Spain, papaya syrup from Florida, taro flour from Hawaii, and soy beans from Manchuria.

Beans and peas. The garbanzo or chick-pea makes a tasty and highly nutritious dish. A fine big white bean is the Spanish fava. Unfortunately, a few persons are highly sensitive to it. The soy bean is full of nutriment and recently a way has been found of removing its unpleasant taste. Rowe uses flour made from the lima bean.

Taro. Taro is a big mealy tuber which is one of the most prized foods of the Polynesians. It is now being packed in Hawaii either as a fermented paste or as a powder suitable for the making of mush. This tuber is tasty and highly digestible, and so different botanically from any American food that it should be acceptable to many highly allergic patients.

Breadfruit and bananas. Something might also be done with flour made from the breadfruit, another Polynesian standby. Flour might be made also from dried bananas, and if it should happen to retain some of the glutinous properties of the fresh fruit, it might be useful as a binder to help the baker in making breads without wheat. Much experimenting needs to be done along these lines. The banana can, of course, be used either raw, or better still, cooked.

Rice and barley. Rice, which is the principal food of millions of Asiatics, is one of the best foods that

the allergically-sensitive person can try. Few are unable to digest it comfortably.

Next to wheat, the grain most commonly used in the world is barley. Three species and several subspecies are cultivated. The flour is not glutinous enough for bread-making, and hence through the ages, the grain has been used mainly for the production of beer. Robinson's barley flour makes a delicious breakfast food, and as every cook knows, pearl barley is a good thickener for broths.

Oats and rye. Other flours which are useful sometimes as substitutes for wheat are oats and rye. As yet patients have trouble either in getting these made up into bakery products in pure form, or in eating them as breakfast food without milk or cream. The well-known "rye Krisp" can be of help to the wheat-sensitive person. Robinson's Scotch groats is a very fine, easily digested form of oatmeal.

Millet. Flour made from millet might be tried in the feeding of allergic persons. It was probably the first grain to be used by man, and it still is regarded as an important source of food by primitive peoples in many parts of the world.

Buckwheat, maize, etc. Buckwheat might also be used, as it is not at all related to wheat or to the other commonly used grains. It came originally from the foothills of the Himalayas.

Maize or American corn is an excellent source of carbohydrate and fat, but unfortunately at least one in seventy otherwise normal persons is highly sensitive to it (Hughes), and one in fourteen dyspeptics has some trouble with it (Alvarez and Hinshaw).

An often harmless variety of starch can be obtained from various types of peas and lentils and from the chestnut.

Cassava. Cassava is an important source of food in West Africa, South America, and in several other parts of the world. There are two main varieties, the bitter and the sweet. The white starchy pulp is obtained from large tuberous roots. In commerce cassava starch is sold under the names of "tapioca" or "Brazilian arrowroot." It may well prove useful in the feeding of allergic persons.

Sago. Sago is prepared from the trunks of several species of palms, most of them growing in the East Indies. A form of sago is made also from the pith of a species of Cycas, and all of the varieties are sometimes adulterated with potato starch.

The difficulty in using sago and some of the other starches in elimination diets lies in the fact that cooks are not used to preparing them without adding milk and egg. I find I can give them in apple sauce. Although raw apples are very common producers of indigestion, the cooked apple seems seldom to cause trouble. These starches go well also in mutton broth or lamb stew.

Maple sugar. I sometimes use maple sugar for a day or two as an elimination diet. Few persons should be sensitive to it allergically, but some feel discomfort if they take any considerable amount of any kind of sugar. Possibly when given in concentrated form, it acts as a physical irritant, dehydrating and thereby irritating the gastric mucosa.

Fats. Persons who do not tolerate butter or the now commonly used corn and cottonseed oils and the hydro-

genated fats made from them might experiment with oils obtained from the olive, coconut, peanut, or soy bean, or from sesame or rape seeds. Care would have to be taken to secure these oils unadulterated and untreated with dyes and other substances.

A fine vegetable fat is to be found in the avocado or alligator pear, a fruit which is now becoming cheaper every year as more and more trees come into bearing in the more tropical parts of this country.

Substitutes for breakfast fruit. For those persons who cannot touch citrus fruits or melons, the papaya may come to serve as a substitute. It is not at all related to other commonly used breakfast fruits, but grows on a curious type of palm-like tree. Another food which can sometimes be used with success in elimination diets is pineapple juice.

Source of protein. Persons who are sensitive to beef and mutton might perhaps be able to eat reindeer meat, and it is conceivable that some day they will be eating the canned or frozen meat of sea mammals such as whales, porpoises and seals. Unfortunately, persons who are sensitive to fish seem often to be sensitive to every variety they have ever tried.

Those who cannot touch cow's milk can secure goat's milk in cans, and artificial milks are being made from such foods as soy beans and almonds. Already there are several substitutes for butter on the market, but fortunately, only the most extremely milk-sensitive persons need to use them.

Importing houses. Fortunately in large cities where there is a large immigrant population there are stores where one can buy almost every type of food known to man. From now on, these stores are likely to be patronized not only by women with shawls over their heads, but also by sufferers with allergic diseases.

SUMMARY

In the beginning, allergists had to be mainly concerned with the taking away of foods. Now more attention must be paid to the replacing of the hurtful foods with harmless ones. The problem of doing this is often difficult. Some highly food-sensitive persons could be saved from much distress if all the constituents of processed foods were listed on the label.

Approximately 60 per cent of Americans are somewhat food-sensitive, and perhaps 2 per cent are highly food-sensitive.

There is need in all large cities for bakeries that will supply breadstuffs made without wheat, egg or milk.

It is probable that many highly food-sensitive persons could widen their diets by searching the world's markets for new foods. Suggestions have been made as to some of the foods that might be tried. Research needs to be done also to see if some foods could be detoxified or in some way rendered harmless to sensitive persons.

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A useful book for those who want to study the foods of other lands is "Geographie und Geschichte der Ernährungs" by K. Hirtle, published by Georg Thieme, Leipzig, 1934.

Peritonitis Due to Ruptured Acute Appendicitis in Children; Influence of Delay on the Operative Mortality*

By

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EARLY diagnosis and efficient treatment will undoubtedly lower the mortality in acute appendicitis; about this there is general agreement. Education against the pernicious prevalence of purgatives is another factor which must be emphasized. If the excessive number of ruptured appendices coming under our care were reduced or eliminated, there would probably be a scant 1,000 rather than the toll of 20,000 deaths each year from acute appendicitis. Until this time occurs, every surgeon is confronted with patients whose appendix has already ruptured and who present manifestations of peritonitis, local or general; it is almost entirely in this group that the fatal cases occur, and the problem of reducing the mortality is an urgent one. This is especially true of children; the present report is concerned only with patients under 14 years of age.

There are in general two points of view in regard to the operative therapy in patients with peritonitis from ruptured acute appendicitis. One group of surgeons urges immediate operation in order to reach the lesion as soon as possible and to remove the source of the infection by appendectomy. The second group takes the stand that postponement of operation allows the infection to become more localized, increases the resistance of the patient, and results in a lower mortality. The study upon which the present paper is based comprises patients treated according to both points of view. An analysis of the results has proved illuminating because of the definite differences in the findings in each group.

PREVIOUS OBSERVATIONS

In spite of the tremendous literature on the treatment of acute appendicitis, it is difficult to gather direct data, in children at least, on the relation between mortality and the period elapsing between admission and operation. With many instances the reports comprise both adults and children; because the situation in children is always more serious and the progress more rapid, the question of deferred operation may perhaps be answered differently depending on the age of the patient. In those surgeons advising the deferred operation, moreover, no mention is often made as to the extent of delay, although where the Ochsner treatment is designated, presumably a lapse of several days at least is indicated. An excellent statement of the confused status of the literature will be found in a paper by McKenty (1).

As an advocate of the deferred operation in spreading peritonitis, Coller and Potter (2) find their mortality greatly reduced since this policy was adopted,

from a very high figure to 9.3%. Of those under 16 years of age, the mortality was slightly higher, 12.5%. Horsley (3), on the other hand, advises immediate operation, reporting a low mortality of 3.1% in patients with peritonitis; no figures are given in regard to the deferred operation, since this procedure was not carried out.

Turning to the opposite side again, Guerry (4) reports a mortality of 8.2% in patients with diffuse peritonitis operated upon at once; with the deferred operation (Ochsner therapy), the mortality was 1.6%. He is therefore an enthusiastic advocate of the latter policy. Stanton (5) reports similar findings; neither of these authors have classified their patients according to age. Pattison (6), though reporting no data on the question of deferred operation, advises immediate operation in every case of advanced peritonitis as long as the patient is in good condition; conservative therapy is relegated to those who are in any degree of shock on admission. A similar point of view is expressed by Maes and McPetridge (7) who adopt the expectant treatment in adults with many misgivings, but do not even consider it in children; they report no data on this point. Keyes (8) and Stone (9), who made extensive studies of acute appendicitis in children did not go into the question of the immediate vs. delayed operation. In the British literature there is a similar, though perhaps more sharp difference of opinion. In general, therefore, it is difficult to draw accurate inferences from most of the cases reported. For this reason no résumé is attempted; the data herein is therefore presented without further reference to those of others.

COMMENT ON PRESENT FINDINGS

The clinical data for this study were obtained from consecutive admissions to the St. Louis Children's Hospital up to January 1, 1936; all cases were selected with a final diagnosis of acute appendicitis with rupture resulting in a local or general peritonitis. All of the patients were operated upon, and the anatomical diagnosis was based on the findings at laparotomy. On this basis the collection of the cases was nearly always easy; in only a few cases was an actual peritonitis present with an unruptured appendix; these were excluded. On the other hand, a few patients had a definite local or general peritonitis, although the appendix was not found; these cases were included if the origin of the infection seemed definitely appendiceal. No attempt was made to divide the cases into those with local and those with general peritonitis; this was often difficult clinically and sometimes impossible, even at laparotomy. It was a frequent experience to find the lesion at operation quite different from the one expected clinically. For example, a mass, supposedly an abscess, would prove to be indurated

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omentum surrounding an appendix which was not even ruptured. Again, the abdominal signs would suggest a diffuse peritonitis, whereas at operation clear fluid would be encountered in the general peritoneal cavity with pus localized about the appendix. On the other hand, a mass which was actually due to an abscess was often found to be associated with a general peri-

course of the infection. However, it is difficult clinically to tell just when the appendix has ruptured; this is in contrast to the exact determination of when the appendicitis started. These considerations are important, because they have a bearing on the decision of the surgeon as to the proper time for operation once a peritonitis is present, or presumed to be present.

CHART 1

Mortality of all "ruptured" cases arranged according to the time of operation

	Hours elapsing between admission and operation							Total
	1	2-1	5-7	9-11	12-18	18-24	Over 24	
Cases	17	114	7	5	8	13	17	181
Deaths	4	14	2	2	1	1	4	28
Mortality	26%	12%	30%	40%	12%	8%	23%	15.5%
138 cases mortality 14.5%				43 cases mortality 18.5%				

tonitis because pus had burrowed through and broken into the general peritoneal cavity. This discrepancy between the bedside impression and the operative findings is especially true in children, as most observers agree. For these reasons it was felt that no practical advantage would be gained by such a classification, at least as far as the present discussion is concerned.

In all, 181 patients were studied; these were first arranged according to the time elapsing between admission and operation, and further subdivided into two groups, the "toxic" and "non-toxic." The separation into two groups in these children was not particularly difficult and was based to a large extent on the observations of the pediatric staff. No arbitrary elevation in the temperature or pulse rate was taken, although the children who were obviously very ill always presented a high fever and fast pulse. In most cases, however, the general appearance and behavior of the child was more indicative of toxicity; the existence of severe prostration was always assumed to be of great significance. There were 33 patients in the "toxic" group; the remainder were classified as "non-toxic." It might be assumed that the difference in the toxic manifestations were always due to a difference in the duration of the disease. This was not necessarily true, however. Many of the very toxic patients had taken ill but 21 to 48 hours before admission, whereas a number of those in the "non-toxic" group presented a history of several days since the onset of the attack. It must be assumed that the virulence of the organism or organisms played an important role in the severity of the general reaction. This conception fits in, of course, with experience in other types of serious infections which threaten life. It has become the custom to correlate mortality in acute appendicitis with the duration of the disease. This is true, if one considers *all* cases of acute appendicitis, both ruptured and unruptured; obviously, any delay immediately following the onset allows rupture to occur and will increase the mortality tremendously. Once rupture occurs, the duration of the disease still plays an important role in the mortality, but the virulence of the organism invading the peritoneal cavity probably plays an equal, if not a greater part in the

The accompanying charts reveal the main findings and really require little additional explanation. It will be noted that the mortality of the whole group was 15.5%; in the "non-toxic" group, however, only 6% died, whereas of those entering the hospital with "toxic" manifestations, 57% succumbed. In Chart 1 all cases are arranged according to the hour of operation; the mortality shows no consistent trend in the various groups operated upon at various intervals following admission. In the great majority of these patients, to be sure, operation was carried out within a few hours; this, indeed, was the usual policy. In the others, the delay was often a matter of extraneous circumstances. In a few cases it was due to difficulty in getting permission from parents or guardians; in many, however, the question of diagnosis was responsible. In general, they form such small groups that little significance need be attached to their differences in respective mortality. It should be noted, however, that, taking all cases, there seems to be no progressive lowering of the mortality with increasing delay; indeed, a mortality of 14.5% was present in those operated on within 8 hours following admission, whereas of those operated on after 8 hours 18.5% died. This difference is too small, however, to assume much significance from statistical point of view.

Much more decisive findings are observed if one separates the cases into the "toxic" and "non-toxic" groups. Thus, in the "toxic" group, the period of time elapsing between admission and operation seems of definite significance. (See Chart 2). A mortality of 70% in those operated on at once in contrast to a figure of 30% in those operated on 9 to 21 hours later indicates the value of delay in this type of patient. The reason for this difference is easy to understand and becomes obvious when one considers the fundamental considerations in regard to the operability of very sick children. Most of the children in this "toxic" group were extremely dehydrated from incessant vomiting; many had been ill-treated in the home; they had been given repeated cathartics and other medication, had had no rest, and in many cases had traveled a long distance, often without provision for recumbency. It is not surprising that such a child, if taken

to the operating room and given a general anesthetic, will almost surely die. On the other hand, if the child is put to bed, given good nursing care, dehydration corrected by parenteral fluids, rest achieved by physical or pharmacological means, dilatation of the stomach relieved by gastric lavage, transfused if

CHART 2

Mortality of "toxic" cases arranged according to the time of operation

	Cases	Deaths	Rate
Operation 1 to 8 hours* after admission	23	16	70%
Operation 9 to 48 hours** after admission	10	3	30%
Total	33	19	57%

*Most of these patients were operated on within 3 hours after admission.

**Only one patient was operated on 48 hours after admission, because he also had measles, which was largely responsible for the fatal outcome 2 days later.

necessary, fecal impaction eliminated—if all these procedures are carried out, and the operation then performed, after the general condition has improved sufficiently to permit it, the mortality will be cut to less than half.

In the "non-toxic" group (see Chart 3) the findings are the reverse of those in the "toxic" group, i.e., the mortality was lowest (3.5%) in those operated upon within 8 hours after admission, whereas it was four times greater (15%) in those operated upon 8 hours or longer after admission. Thus, in patients entering the hospital in good condition, delay increases the likelihood of a fatal outcome considerably. This is not surprising, for it bears out a fundamental principle,

CHART 3

Mortality of "non-toxic" cases, arranged according to time of operation

	Cases	Deaths	Rate
Operation 1 to 8 hours after admission	115	4	3.5%
Operation 8 hours or longer after admission	33	5	15%
Total	148	9	6%

i.e., that where the source of a peritonitis can be eliminated safely, the earlier it is done the more likely is the infection overcome.

The type of anesthetic and the operative procedure itself undoubtedly play important parts also; these factors are not considered in this report. In general, the cases herein described were all operated upon by the same group of surgeons, using a similar technic and the same anesthesia and anesthetists. Differences in mortality are referable therefore to the other factors mentioned, notably the period of time elapsing between admission and operation.

Comparison of the findings in Charts 2 and 3 leads to certain clear-cut inferences. If a child enters the hospital prostrated, dehydrated, toxic, obviously unfit for an operative procedure, delay is indicated, regard-

less of the period of time the child has been sick. How long the delay should be cannot be answered from the present findings, because, with one exception, operation was not deferred beyond 24 hours. Although the mortality was less than half in those operated on after a delay of more than 8 hours, it might be argued that the mortality might have been still lower if 36 or 48 hours or more had elapsed before laparotomy. This point cannot be answered on the basis of the present findings. Certainly, however, the advantage of delay in order to make the patient more able to withstand operation is clearly shown and should be emphasized. If a child is not toxic, however, the necessity of immediate operation is indicated by the increased mortality in those operated on after a delay of 8 hours or more. These differences in mortality may be graphically expressed as follows:

Toxic cases: mortality of operation within 8 hours of admission 70%
 Toxic cases: mortality of operation after 8 hours 30%
 Non-toxic cases: mortality of operation within 8 hours of admission 3.5%
 Non-toxic cases: mortality of operation after 8 hours 15%

The danger of a policy of unqualified delay is obvious from these findings. Unfortunately, the idea that delayed operation is advantageous in peritonitis from acute appendicitis with rupture has been accepted by a good many physicians without regard to the potential harm of such an inference. This is particularly true when applied to the care of such patients in the home. The necessity of early diagnosis and treatment of acute appendicitis in a hospital cannot be too strongly emphasized. If delay is advisable, the decision should rest with a competent surgeon; under such circumstances the patient is enabled to receive the necessary care which delay justifies. Indiscriminate advocacy of delay may be partly responsible for the unfortunate increasing mortality in acute appendicitis. The general practitioner has heard his surgical colleagues speak of the advantages of the so-called Ochsner therapy, and as a result he is tempted to follow this advice whenever he is confronted with a case of acute appendicitis. He does not realize that this type of expectant or non-operative therapy is reserved for a really small percentage of patients with peritonitis; indeed, patients who should not have been permitted to develop peritonitis. Moreover, it is occasionally difficult to tell clinically, even by an experienced surgeon, whether there is a peritonitis and whether it is spreading or not. From the findings herein presented, the necessity of immediate operation is clear whether the appendix is ruptured or not, whether a peritonitis is present or not, provided the child is in a good condition to withstand the procedure. If the child is not in such a state, delay is advisable; such delay is valuable because it enables the surgeon to carry out non-operative therapeutic procedures which improve the general condition sufficiently to permit operation for elimination of the source of the infection and in certain cases to allow localization of the infection to take place. Thus the question of immediate or deferred operation is answered not so much by an estimate of the extent of the lesion, but upon the extent to which the lesion has affected the general condition, i.e., the operability.

CONCLUSIONS

The evidence herein presented indicates that children with acute ruptured appendicitis entering the hospital in good general condition should be operated upon at once. Thus the treatment is the same as that of unruptured acute appendicitis. In contrast, those entering the hospital severely ill should not be operated upon at once, but only after a delay, which is utilized in improving the general condition of the patient by correcting dehydration, relieving distension, achieving rest, giving transfusions, etc., and in some cases long enough to allow localization to occur. The decision as to delay should not be made in the home, but while the child is in the hospital under the care of a competent surgeon. On the basis of the present findings it would seem that the problem of the deferred operation depends not so much upon the presence or absence or degree of peritonitis, which may be difficult to estimate accurately at the bedside, but upon the general condition of the child, i.e., the operability. In any case, the necessity of hospitalizing

every child with acute appendicitis is clearly indicated; immediate or delayed operation can best be determined "on the threshold of the operating room."

SUMMARY

1. In 181 children operated on for peritonitis following rupture of acute appendicitis, operation was fatal in 28, making the mortality 15.5% of the 181 children, 33 entered the hospital extremely ill ("toxic"); 19 of these patients died, making the mortality 57%. In the remaining 148 ("non-toxic") patients, 9 succumbed, making the mortality 6%.

2. In the 181 patients as a whole, no definite correlation could be found between mortality and time elapsed between admission and operation.

3. In the "toxic" group, the mortality was 70% in those operated upon at once, and 30% in those operated upon after a delay of 9 to 24 hours.

4. In the "non-toxic" group, the mortality was 3.5% in those operated upon at once, 15% in those operated upon after a delay of 9 hours or more.

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A Report of Ten Cases of Pellagra Treated with Nicotinic Acid

By

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FUNK in 1911, 12, 13, stated that his II factor C₁₂H₁₀O₂N was nicotinic acid which was isolated from rice polishings and yeast. It had by itself no therapeutic action in treating polyneuritic pigeons but did augment the actions of the other fractions. His I fraction from yeast caused improvement in polyneuritic birds, while the I and II fractions cured them readily, thus, showing that nicotinic acid or II greatly augmented the action of I. When all three fractions were added even greater improvement was noted. This work was later confirmed by Szymanska and Funk and Casimar Funk.

In 1918, Golberger, Wheeler and Sydenstricker (1), after considerable experimentation, declared that pellagra as the disease is known, was a fusion of two closely related syndromes with possibly two separate factors as the cause. Elvehjem, Madden, Strong and Wooley (2) in September, 1937, reported that nicotinic acid would cure black tongue in dogs. Street and Cowgill (3) confirmed these findings while Chick, Macrae and Martin (4) cured black tongue in swine. Sebrell, Onstott, Fraser and Daft (5) found that 6 mg. of nicotinic acid twice a week would prevent the disease in dogs on a pellagra producing diet. Spies, Cooper and Blankenhorn (6) treated four cases of human pellagra while Fouts, Holmer, Lepovsky and Jukes (7) reported that 500 mg. of nicotinic acid was not as

good as liver filtrate. Harris (8) reported improvement in five cases treated with nicotinic acid. Spies again recommended that the patient be given a well balanced diet with nicotinic acid. Smith, Ruffin and Smith (9), added a case, and suggested nicotinic acid in drinking water as a pellagra preventing caution. Sebrell and Onstott (10) found that dogs, on a black tongue producing diet while taking nicotinic acid will die if riboflavin is absent.

METHOD OF STUDY

The ten pellagrans selected for this study had a symmetrical dermatitis characteristic of the Golberger type, with the exception of Case 7, who gave a history of dermatitis, but at the time of the study, was entirely free. Patients having a secondary type of pellagra due to organic disease, were carefully excluded, and none gave a history of chronic alcoholic addiction. There was included one case (Case 1), whose chief complaint was a thick leathery dermatitis on the backs of both hands with moderate abrasions. There were three cases presenting a dermatitis on the back of the hands, with thick indurated skin without abrasions (Cases 2, 9 and 10). Five cases had the acute red dermatitis with thin skin (Cases 3, 4, 5, 6 and 8). The one case of chronic glossitis and stomatitis gave a typical pellagrous history (Case 7).

All of the patients except one (Case 5) were treated ambulatory; however, this case, because of the severe glossitis and stomatitis, was unable to swallow food, and was, therefore, on a deficient diet. No changes were made

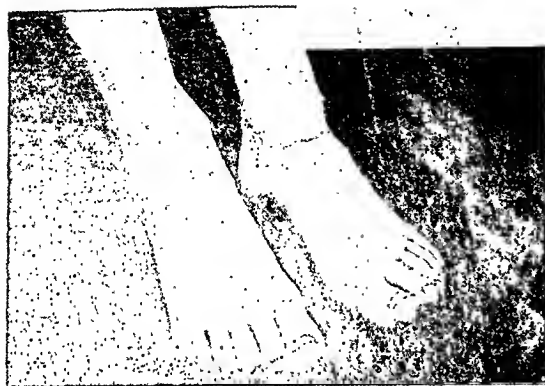


Fig. 1. The "Pellagrous Boot" of Case 6 before treatment was instituted.

in any of the patient's diets and the environment was unchanged. Their diet deficiencies were confirmed during the course of treatment. Organic disease was ruled out by thorough physical examination, laboratory tests and X-ray examinations. No other medication except nicotinic acid was given during the course of observation.

RESULTS

Observations on the chief objective and subjective symptoms are summarized as follows: It was noted that patients with thin skin, who had the typical pellagrous dermatitis, responded to treatment with nicotinic acid within ten days (Cases 3, 4, 5, 6 and 8). Subjects (2, 9 and 10), with the thick dermatitis, showed improvement and cure in two months. Subject (1) took 76 days to completely clear the abrasions.

The stomatitis and glossitis gave the quicker response to treatment with nicotinic acid, the mouth being clear two or three days before the dermatitis subsided (Case 3, 4, 5 and 9). The stomatitis of (Case 7) had been present for two years and responded much more slowly than the more acute types. The tongue in this case was atrophic, thickened, beefy red, and stiffened. Satisfactory response in 36 days required rather large doses of nicotinic acid.

The diarrhea was controlled in (Case 2) in three days with 50 mg. of nicotinic acid a day; however, it recurred again on the 14, 15 and 16th days when 100 mg. of nicotinic acid was being given. When this patient ran out of medicine on the 50th day, the diarrhea recurred on the 52nd day and continued until administration of 200 mg. per day. It again recurred on the 66th day after 200 mg. of nicotinic acid per day had been given for six days. The diarrhea of (Case 8) was controlled with 50 to 100 mg. of nicotinic acid a day, but recurred on the 32nd, 33rd, 34th, 35th and 36th days while 150 mg. was being taken. The diarrhea of (Case 8) was controlled readily with 50 mg. of nicotinic acid but recurred on the 30th day under administration of 150 mg. and again on the 42nd day under administration of 300 mg. The diarrhea of (Case 10) responded slowly to 100 mg. of nicotinic acid, taking ten days. It recurred again on the 22nd, 23rd, 24th, 25th and 26th days while 150 mg. was being administered a day. It also broke through on the 40th, 41st, 42nd, 43rd, 45th and 46th days on 150 mg. per day. Since this work has been completed, we have observed a patient whose diarrhea recurred on 600 mg. per day.



Fig. 2. The dermatitis of Case 6 on the tenth day of nicotinic acid therapy.

It was noted that the neuritis of (Cases 1, 2, 5, 7 and 10) was slightly improved while (Cases 3 and 9) became progressively worse. Although (Case 3) had no neuritis at the beginning of treatment, she developed, on the 36th day while 150 mg. were being administered a day, a rather severe generalized neuritis.

The general health was slightly improved in (Cases 1, 2, 3, 5, 7, 8 and 10) while (Cases 4, 6 and 9) showed no improvement or became slightly worse. (Case No. 9's) general condition became critical when he developed attacks of angina pectoris.

None of the cases had severe mental disturbances except (Cases 5 and 10). (Case 5) was acutely delirious. This quickly cleared following 100 mg. for three days. However, her memory and neurosis remained unchanged. (Case 10) had had severe mental symptoms with institutional care ten years previous. He now elicited a rather severe neurosis bordering on psychosis. He was benefited approximately 25% in two months.

REACTIONS FROM NICOTINIC ACID

Approximately 2,500-50 mg. nicotinic acid tablets and 300-100 mg. tablets were given to 31 pellagrins over a period of two and one-half months. No severe reactions occurred. The flush, tingling, and a sensation of heat to the skin of the face and arms was noted in most of the patients. 600 mg. of nicotinic acid a day have been given with no untoward reactions. All of the drug was administered by mouth. Burning of the stomach was quickly relieved by drinking water in sufficient amounts with the medicine.

CONCLUSIONS

First: Nicotinic acid, 50 mg. to 500 mg. per day, is specific in curing the acute dermatitis and glossitis of the Golberger type of pellagra.

Second: Prolonged use of 150 mg. to 500 mg. of nicotinic acid a day will cure the chronic dermatitis with abrasion and chronic glossitis of typical pellagra.

Third: Nicotinic acid in doses up to 500 mg. will partially control the diarrhea of typical pellagra.

Fourth: Nicotinic acid from 50 mg. to 500 mg. a day is of very little aid in the treatment of the neuritis and mental symptoms associated with pellagra in humans except those with acute delirium.

Fifth: The general health of the pellagrous patient

is only slightly enhanced by treatment with nicotinic acid (50 mg. to 500 mg. per day).

Sixth: There is probably another factor or factors,

other than nicotinic acid, which is necessary to completely cure the human pellagrous patient.

Nicotinic Acid furnished by Abbott Laboratories.

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Studies on Water and Soap Enemas*

By

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THE Egyptians are said by Pliny (1) to have discovered the effect of enemas or clysters from the act of a bird called the ibis. "He washes the inside of his body by introducing water with his beak into the channel by which our health demands that the residue of our food should leave." The idea was probably obtained from the bird's habit of collecting oil from the preen-gland, situated close to the rump, with its long curved bill which it frequently dipped into the water as it preened its feathers. Evacuation of a liquid feces was probably often associated with the act of preening. These two acts were then correlated by the Egyptians and since they knew nothing of the preen gland nor of the common passage of urine and feces through the cloaca an erroneous conclusion was reached.

After the Renaissance, enemas became extremely popular as a general health measure but with the closing of the eighteenth century they became less a fad with the laity and more of a therapeutic agent among physicians. The chief interest became centered about the quantity, constituents and methods of administering enemas (2).

At the present time, enemas have a definite place in clinical medicine and yet much work needs to be done to determine the mechanism of action by which the various types elicit their results. Since colon activity, especially peristalsis, is usually considered an important mechanism in defecation our study has been limited to the circular muscle activity. In order to obtain records simultaneously from several parts of the colon a tandem balloon system (3) was used as modified by Templeton and Lawson (4) for the purpose of correlating proximal and distal colon activity.

A tandem system consists essentially of three bal-

loons arranged in linear order and connected by rubber tubes to respective manometers. The tubes fitted with coil springs to give the desired rigidity are fastened together with rubber cement. To make the compartments leak-proof, a base of rubber cement is molded about the tubes where the balloons are to be tied. Special balloons* 5 cm. long and 5 cm. in diameter at the center and tapering to 2 cm. in diameter at the two open ends are used. When completed the entire set is 20 cm. long with three compartments of 3 cm., each separated from one another by 5 cm. and a terminal 1 cm. which serves as a guide for insertion.

The manometer floats are simply inverted Wassermann tubes (5) with capillary glass uprights attached to their closed ends. Such floats can be sunk to the desired level simply by the quantity of manometer fluid held in the tube. The manometer caps (2 cm. tall) are held snugly against the manometers by means of a thin copper sheet inner lining. Celluloid elbows are used to connect glass writing points to the uprights. The points are held against a smoked drum at the desired tension by means of a glass upright attached to each brass cap by a flexible spring (6). Two tandem systems of three balloons each were used in this study enabling us to record simultaneously, activity from six segments of the gut. A special clamp (6) was designed to hold the desired number of manometers in such relation to each other that all could record in a vertical line.

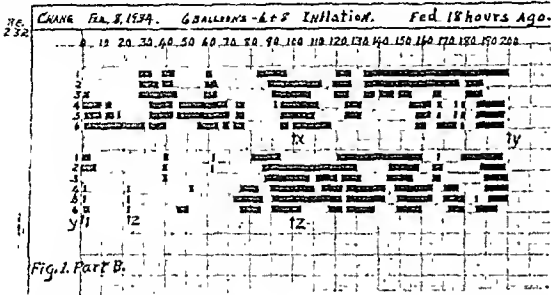
For this study only trained cecostomized dogs were used. The dogs were taught to lie quietly with only a blind over their eyes for the length of time required for the experiment (up to 20 hours). One set of balloons, called the proximal set, was inserted through the cecostomy, and the second set by way of the anus.

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Submitted August 8, 1938.

*Manufactured by Acme Rubber Co., Masillon, Ohio, (formerly by the Hankins Rubber Co.).



Fig. 1. Part A. Two hundred minutes of a six balloon tracing. X to Y, control period of 100 minutes. 1, injection of 50 cc. of soap solution per rectum. 2, repetition of 1. Y to Z, 100 minutes of tracing following retention enema.



Part B. Diagrammatic graph of entire six balloon tracing of which an excerpt of the original is given in part A. X to Y corresponds to X to Y in part A. 1 and 2 represent 1 and 2 in part A. Y to Z corresponds to Y to Z in part A.

When in position, the balloon systems were tied in place by a rope harness about the dog's body.

The quantity of activity within any given time may be measured by the amplitude of activity or by the time spent in activity. The work reported in this paper considers only the latter. Since the colon is essentially periodic (7), it is possible to reproduce the spatial relationship of the active and quiet periods (Fig. 1) on graph paper. To accomplish this, two arbitrary rules were adhered to: First, the gut was considered active if the contraction or contractions lasted one minute or more. Second, the gut was considered quiet if two minutes or more intervened between contractions. By rigidly adhering to these rules the active and quiet periods of the colon were represented in sharp contrast.

In a study of the quantity of colon activity the technical difficulties met with in establishing identical conditions from day to day, make certain variations from a planned routine a likely occurrence. It is necessary, therefore, to know the extent to which colon activity may be influenced by such factors as insertion of the balloons, slight variations in balloon distention, training of the animal, noises, time of feeding, posture of the animal, temperature of the room, sleep, and disturbing stimuli.

Welch and Plant (8) observed a greater tone and activity in the proximal colon of unanesthetized dogs during the first portion of the tracings. Lawson and Templeton (9) observed irregularities in the first portion of the tracing similar to those of Welch and Plant. In general, our observations agree with the previous authors. Although the total activity of the entire colon in the first 50 minutes of an experiment is more irregular than that in the succeeding period, the difference is not sufficiently marked to require

discarding the first portion of the tracing, when a large number of experiments are performed. This irregularity in the first portion of the experiments is usually attributed to the effect of balloon insertions.

In order to obtain comparable distentions of each balloon and to repeat the same distentions from day to day regardless of the balloon system or animal used, a definite routine was strictly followed. First, only intestinal balloons of constant size (previously described) were used. Second, after the balloons had been inserted and secured in place, they were inflated and deflated several times with the manometers clamped out of the circuit, to smooth out their contour in situ. Third, with the water manometer returned to the circuit, six centimeters of water pressure were drawn against each balloon to insure comparable deflation. Fourth, eight centimeters of water pressure were built up in each manometer and after clamping off the free end of the T tube the positive pressure was then allowed to enter the balloon. Even though the above technique is rigidly adhered to, some uncontrollable deviation in the balloon inflations undoubtedly occur. However, deviations to the extent of 10 cm. of additional water pressure have previously been shown to have only a minor local effect (9). Judging from the character of the tracings obtained from day to day on the same animal or on different animals, any minor variations in balloon distention which we may have encountered, are negligible.

In all of our experiments, at least three weeks were permitted for recovery and training after the cecostomy. At the conclusion of the three week training period, tracings from the colon were obtained periodically. The quantity of activity recorded in the first tracings was not found to consistently differ appreciably from the quantity observed in the same animals two years later.

While training the animals, no precautions were

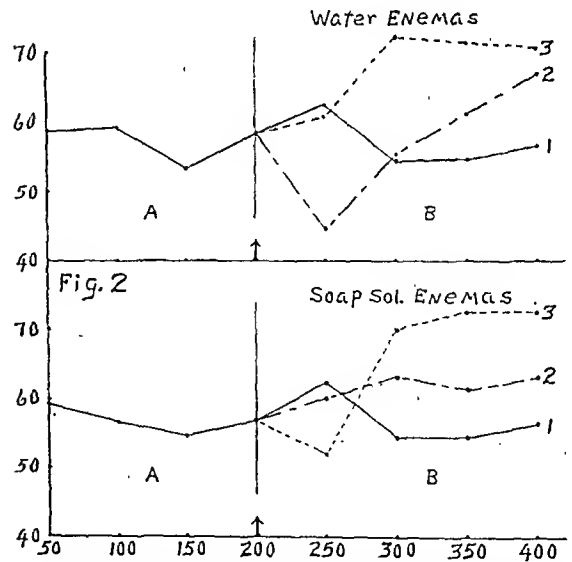


Fig. 2. Continuous experiments (interpretation in text). Average per cent of colon activity per segment. Part A, control period. ↑ = injection of enemas. Part B, after injection of enemas. Curve 1—Control experiments. Curve 2—Following the introduction of 100 cc. enemas. Curve 3—Following the introduction of 200 cc. enemas.

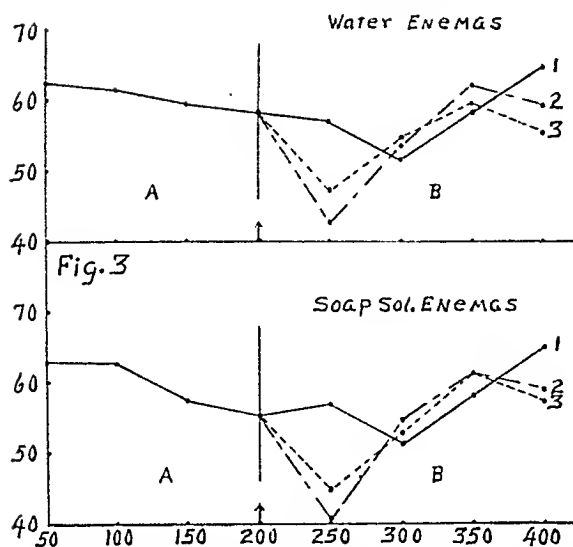


Fig. 3. Interrupted experiments (interpretation in text). Labeling as in Fig. 2.

taken to exclude the ordinary noise met with under laboratory conditions—such as, conversation, movement about the room and so forth. In fact, during the training period, these noises were purposely exaggerated. Following such training, it was not possible to differentiate by a careful study of the record, when people were entering or leaving or when other ordinary noises occurred in the laboratory.

The influence of feeding the animal or filling the stomach has been studied by various investigators (8, 10, 11). Our observations were made 12 to 24 hours after the ingestion of food. The food consisted of about 5 pounds of a mixture of ground beef lung and white bread in proportions of 4 to 1 by weight, to which 50 grams of bone were added. No significant difference was observed in the quantity of colon activity recorded within the confines of this period.

In the majority of our experiments, the animals were kept lying comfortably on their side throughout the course of the observations. Some experiments, however, were obtained with the animals standing in Pavlov stalls. A comparison revealed no consistent difference in the duration of active periods in these positions, although the amplitude of the contractions was markedly affected.

The temperature of the room in which the experiments were conducted was maintained for the comfort of the animal during the Fall and Winter months; but there existed no adequate means of controlling the temperature during the summer months. Because of this variation it was possible to compare the motility recorded when the animals were panting and when they were more comfortable. Typical tracings under these conditions revealed a difference in character and height of motility, but no appreciable difference in the quantity was consistently related to the different room temperatures.

On many occasions during the course of experiments, animals were observed sleeping as indicated by the type of respiration, snoring, and rapid movements of the paws which occasionally even involved the legs and head, requiring that the animal be awakened to quiet him. During these periods no

change in the quality or quantity of colon activity was observed when compared with the preceding and following activity.

Lawson and Templeton reported that tetanizing currents applied to the distal colon with a strength sufficient to cause signs of discomfort, gave essentially negative results on motility except when the region near the internal anal sphincter was stimulated (9). In our observations, vigorous stimuli applied to the animal's body for admonition were followed first, by contraction of the abdominal muscles, (recorded in the tracing as a sudden rise and fall of the water level in the manometers) and frequently immediately afterwards by simultaneous contractions of all recording segments. In some cases, no other change in the activity was observed; while in others, these simultaneous contractions were followed by a temporary inhibition of activity.

TABLE I

Procedure		Number of Tracings		
		Total	Decreased Activity	Increased Activity
Retained	100 cc. Water	21	17	7
	200 cc. Water	20	9	11
	100 cc. Soap Solution	18	7	11
	200 cc. Soap Solution	19	8	11
Interrupted	100 cc. Water	17	12	5
	200 cc. Water	17	12	5
	100 cc. Soap Solution	18	14	4
	200 cc. Soap Solution	18	13	5
Continuous Controls		24	9	15
Interrupted Controls		18	8	10

Having carefully studied those variations in the experimental procedure which might be encountered in the course of an experiment, the technique employed seemed sufficiently standardized to study the effects of intracolonic injections on large bowel activity. There is, indeed, considerable variation in the quantity of colon activity as recorded by our method from day to day in the same animal. This difference, however, is not explainable on the basis of small variabilities in any of the controllable factors we have studied, thus necessitating several control tracings for each experiment. Especially large differences in the quantity of activity may be seen when the charts of different animals are compared. In one animal the colon may be consistently active less than 50% of the time, while in another activity may be consistently present 75% of the time or more. Naturally such a variability necessitates the use of the same animals throughout the course of any experiment—controls can not be obtained on one animal and the experimental procedure followed on another.

Our selection of substances for intracolonic injections was narrowed to the most commonly used clinical enemas, namely, oil, tap water and soap solutions. In preliminary observations on the relative

efficiency of oil and a one and one-fourth per cent soap solution for eliciting defecation, we found the latter to be much more effective (12), while the efficiency of tap water was found to be comparable to that of the soap solution.

A study of the effect of intracolonic injections on colon motility may be considered from two points of

Only those interrupted experiments were considered in which the animals defecated when given their freedom.

One hundred and fifty-one observations were made on the influence of enemas on the same animals that were used in the control study. Of these, 81 were continuous experiments in which 100 cc. or 200 cc. of

TABLE II
Minutes of activity per 50 minute period

Type of Enemas	Control Period					After Enema Injection				
	Number of Experiments	50 Minute Periods				Number of Experiments	50 Minute Periods			
		1	2	3	4		1	2	3	4
CONTINUOUS EXPERIMENTS										
Control Experiments	71	29.4	29.6	26.7	29.1	27	31.1	27.2	27.3	28.2
100 cc. Water						24	22.2	27.6	30.6	33.1
200 cc. Water						20	30.3	36.0	35.6	35.1
Control Experiments	64	29.6	28.3	27.3	28.4	27	31.1	27.2	27.3	28.2
100 cc. Soap Solution						18	30.0	31.6	30.7	31.6
200 cc. Soap Solution						19	26.0	35.0	36.2	36.2
Control Experiments	69	32.5	31.0	30.0	31.0	24	31.1	27.2	27.3	28.2
100 cc Oil						18	38.4	35.4	35.5	37.2
200 cc. Oil						27	43.2	40.0	38.5	39.0
INTERRUPTED EXPERIMENTS										
Control Experiments	52	31.2	30.8	29.6	29.0	18	28.4	25.7	29.0	32.4
100 cc. Water						17	21.1	26.8	31.0	29.6
200 cc. Water						17	23.6	27.3	29.9	27.8
Control Experiments	51	31.4	31.3	28.8	27.7	18	28.4	25.7	29.0	32.4
100 cc. Soap Solution						18	20.1	27.1	30.6	29.4
200 cc. Soap Solution						18	22.3	26.3	30.6	28.8
Control Experiments	53	34.0	33.4	30.9	32.0	18	28.4	25.7	29.0	32.4
100 cc. Oil						18	30.6	28.9	30.4	30.7
200 cc. Oil						17	32.2	29.7	28.0	29.5

view: 1. the effect associated with the retention of enemas and 2. the residual effect observed after the expulsion of the enemas. The first study, previously reported (13), was concerned with observations on 100 and 200 cc. quantities of white mineral oil. In the continuous experiment, the oil was retained while in the interrupted experiment the animals were permitted to expel the enemas. Under both conditions, but especially in the continuous type, the quantity of activity was observed to be greater following the injection of oil, than in the control experiments.

To control the work on soap solution and tap water enemas, 45 experiments, each of 400 minutes duration, were performed on 4 dogs in which no enemas were given. Of these 27 were continuous experiments in which the animals were kept on the table the entire 400 minutes without removing the balloons. Eighteen were interrupted experiments in which, at the conclusion of 200 minutes, the balloon systems were removed, the dogs allowed their freedom outdoors, and after a 30-minute interval the experiments resumed.

tap water or 1¼ per cent soap solution were injected at the end of a 200 minute control period. The enemas were injected by way of a tube previously fastened on the distal set between the middle and terminal balloons. The animals were not permitted to expel the injected material until the remaining 200 minutes of the experiment were completed. Seventy interrupted enema experiments were conducted in which, at the conclusion of 200 minutes, 100 or 200-cc. of tap water or 1¼ per cent soap solution were injected by way of the previously mentioned enema tube. The balloon systems were then removed, the animals allowed their freedom out doors as in the controls, and after a 30 minute interval, the experiments resumed on those animals which expelled the enema.

It has been common practice to compare the motility immediately preceding an experimental procedure with that which follows shortly afterwards to relate cause and effect. We have therefore, tabulated (Table I) our results to show the number of tracings in which the introduction of enemas was followed by an in-

crease in colon activity for comparison with the number in which a decrease in activity followed the enema administration. In this tabulation, only the 50 minute periods immediately preceding and following the injection of the enema were considered.

In the group of continuous experiments, the introduction of 100 cc. of water on 24 occasions was followed in only 7 by an increase in activity. The administration of 200 cc. of water in 20 experiments was followed in 11 by an increase in activity. The introduction of 100 and 200 cc. of soap solution into the colon in 18 and 19 experiments respectively were followed 11 times each by an increase in activity. These figures indicate that only when 100 cc. water enemas were used was there a decrease in the colon activity in the majority of the continuous tracings. A decrease in activity, however, was observed in more than two-thirds of the interrupted experiments whether water or soap solution in 100 or 200 cc. quantities were used. This method fails to consider the degree of increase or decrease in activity and does not take into consideration the expectancy curve which is obtained from control experiments in which no enemas were introduced. A study of comparable time periods in control tracings revealed an expectancy increase in activity in 15 of 24 continuous experiments, and in 10 of 18 interrupted experiments.

The average percentage of activity in the experimental groups compared to the control group is probably more significant than the fact that some degree of increase or decrease in activity followed the administration of an enema in a certain number of experiments.

In the continuous experiments (Fig. 2) during the first 50 minutes following the enema injection, the average activity was below that of the controls for the same period. During the next 50 minutes the per cent of activity in all experimental groups rose toward or actually above that of the control group. In the last 100 minutes, the quantity of activity in the experimental groups was well above that of the controls.

In the interrupted experiments (Fig. 3) where either tap water or soap solution was used the effect was practically the same, whether in 100 or 200 cc. quantities. During the first 50 minutes following the administration, activity was below that of the controls. In the next 50 minutes, the percentage of activity in all groups returned to approximately that of the controls and became for the succeeding 50 minutes slightly above the control level. During the last 50 minutes, the per cent of activity in the experimental groups again dropped below that of the control level. Our observations are not in accord with those of Yamamoto (14), who reported, from roentgen ray studies, an acceleration of the movements of the colon following soap water enemas. We are not able to interpret the efficiency of soap solutions in eliciting defecation as Hurst does (15), on the basis of increased peristalsis.

In all experimental results whether the procedure involved continuous or interrupted experiments, soap or water enemas, in either 100 or 200 cc. quantities, the percentage of activity of the first 50 minutes was less than that observed in the respective control experiments. In direct contrast to this, we reported that oil enemas whether in 100 or 200 cc. quantities, in continuous or interrupted experiments caused an in-

crease in activity above the controls which reached a peak in the first 50 minutes (Table II).

If high activity is an index of a defecation urge, the augmentation following oil, reported by us, should be associated with a higher percentage of defecation than soap or water. Since the reverse is true, namely, soap solution and tap water are more efficient in eliciting defecation, it is apparent that, under these conditions, the defecation urge is associated with the less active colon.

In the light of these results and those previously reported (16), we may consider enemas as having at least two actions. First, an effect on colon activity, and second, an initiation of the defecation urge. These two actions may conflict under experimental conditions. If the stimulus to defecation is excessively strong due to the character of the enema and the animal is under conditions not customarily associated with defecation, the act may be inhibited. Such inhibitions may serve also to decrease the activity. On such grounds the *modus operandi* in the depression of activity obtained with soap and water enemas during the first succeeding 50 minutes following injections may be explained. On the other hand, the stimulus to colon motility may be moderately strong and yet elicit only a mild defecation urge. Under such conditions, the colon activity may rise above the control level, as reported by us with oil enemas, without initiating an inhibitory mechanism to that motility.

It is possible that the inhibition of circular activity is more frequently associated with the urge and the act of defecation than is an augmentation of such activity. Relaxation of the gut may elicit a defecation impulse by a mechanism similar to that by which distension acts. Defecation may then be a voluntary act in which the contents of the distal colon are forced through the relaxed tube.

SUMMARY

1. The balloon technique for the study of colon motility is discussed.
2. The influences of extraneous factors commonly encountered in an experiment are discussed.
3. Enemas of soap solution or tap water were found to be more efficient in producing defecation than white mineral oil.
4. For the purpose of quantitating colon motility, first, the active and quiet periods are shown in sharp contrast, and second, the time spent in activity is expressed on a percentage basis.
5. During the first 50 minutes following the administration of soap or water enemas, in the continuous experiments, the percentage of activity was found to be less than that of the controls.
6. In the interrupted experiments, when expulsion of the enema was permitted, a similar but more lasting decrease in colon activity was observed than in the continuous experiments.
7. The decrease in colon activity associated with soap or water enemas is in marked contrast to the results previously obtained with oil enemas.
8. Under the experimental conditions used in this study, soap solution and tap water enemas were found to exert comparable effects on colon activity.

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Anorexia and Gastric Motility*

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THE experimental work presented in this paper was undertaken for the purpose of determining the relation between gastric motility and anorexia in children. The frequency with which this type of disorder comes to the attention of physicians has been investigated by Bartlett (1928). Of the children attending an outpatient department, 24% were anorexic and a third of these showed no lesions which might account for the difficulty. They were classed as cases of functional anorexia when they showed definite signs of malnutrition as well as being reported poor eaters by the parents. Investigators (Moseley, 1925; Johnston, F. A., 1926; and Dumond, H. E., 1928) who visited homes in both city and country communities reported "non-hunger" in 2/3 of the city children, who were a group living in comfortable homes, and in only 1/3 of the country children. Only 5% of city children by Stolz (1934) gives information on both the frequency of occurrence of anorexia and also on its persistence in a group of children in their 2nd year of life. Information was obtained from the mothers' reports. At 21 months of age 11% of the group was anorexic and at 36 months, 26% of the group was anorexic. No child was reported as showing anorexia evidence on the persistence of good or poor appetite is given (Thurston, 1929) in a report on the time taken by nursery school children to eat a standardized meal. The author states that "a study of the individual children shows no consistently fast or slow eaters, and there are only 14 of the 41 children who tend to be consistently average." Davis, C. M. (1928) in a study of self-selected diets by infants of weaning age also mentions the variability of appetite. The above studies indicate that though a fairly large number of children in the groups studied showed anorexia, repeated observations showed persistent anorexia to be relatively uncommon.

CAUSATION

(1) One of the most frequent explanations of anorexia in children, when it is not associated with diseased conditions, is that the child has developed poor eating habits. (Abt, 1924) (Porter, 1925). Aldrich (1925), presents the view that anorexia frequently develops in children when

the parents attempt to force them to eat definite amounts and kinds of food, often in an attempt to make them attain a certain standard of height and weight. He presents evidence from a questionnaire study tending to show that anorexia does not develop where parents have been instructed not to force children to eat. Johnston (1926) discussing the studies previously mentioned on city and country children, attributes the higher figures for "non-hunger" found among city children as compared with rural children, to the greater prevalence of over-solicitude among city mothers.

(2) Other writers who agree with the first group that poor eating habits are responsible for anorexia, make the additional point that physical consequences of the low food intake often intensify and prolong the state of anorexia. Venables (1930) states that anorexia is due to psychological causes, but is perpetuated by such factors as constipation, feelings of discomfort, distention and nausea on taking food. He reports favorable results with forced feeding to restore the normal eating habit in adult cases. Langdon Brown and Crookshank (1931) report similar observations. Kugelmass and Samuel (1931) believe that anorexia is due to emotional disturbances or other psychological causes which in turn produce functional atony of the gastro-intestinal tract, constipation and other symptoms, including anorexia. No direct evidence on the motility of the gastro-intestinal tract is given either before or after their dietary treatment of anorexic children, so that it is not possible to verify the assumption that an atonic condition of the gastro-intestinal tract existed or that any change in the tonicity was brought about by the dietary treatment.

(3) A third group of writers may be placed together in assuming that some constitutional defect is primarily responsible for anorexia observed in children. A frequently mentioned factor of this type is a gastric atony which is thought to be one manifestation of a type also characterized by a generally poor muscular development, associated with a frail body build. Anorexia, poor nutrition, and a tendency toward digestive disturbances are thought to result from the gastric atony. Rupp and Schlutz (1930) studied the motility of the empty stomach in normal and in malnourished asthenic children. The authors conclude that the normal children's stomachs exhibit greater activity in terms of length of an activity period, than those of subjects with a frail asthenic build, and that among the latter group those with anorexia and other gastro-intestinal complaints showed the least gastric activity. The authors recognize that the conclusion

tentative since they are based on only two selected records from each child. Lucas and Pryor (1931) report an association between anorexia, constipation, poor nutrition and a slender type of body build, though the precise relationships are not stated. Gastric atony is assumed but no observations on the motility or tonicity of the gastro-intestinal tract are made.

There is on the other hand evidence which conflicts with the view that anorexia is characterized by decreased gastric motility. Taylor (1917) found the contractions of the empty stomach in infants who nursed feebly were of normal intensity. In other types of mild disturbance where the usual sensations of hunger and appetite are absent, there is no depression of gastric motility. Carlson (1916) states that accompanying moderate degrees of fever there are "objectively normal gastric contractions parallel with the epigastric feeling of 'sick stomach,' nausea, headache, depression, no thought of or desire for food." Smith (1927) states that in the early stages of Vitamin B deficiency where animals had shown anorexia for the Vitamin B deficient diet for four days, the hunger contractions were not distinguishable from those of normal dogs. It is significant that moderate disturbances accompanied by anorexia may exist without diminution of gastric activity. Presumably the anorexia described in children where there is no obviously diseased condition present, may also be classed as a moderate disturbance, since the children carry on ordinary activities.

EXPERIMENT

The present study was undertaken to obtain evidence on the relation between the so-called functional anorexia in children, and the activity of the empty stomach. Children in the Mooseheart community were first observed to find cases of obvious anorexia, such as might be noticed by a parent in an ordinary community, and might then be brought to the attention of a pediatrician. Observations on some 200 children between the ages of 9 and 15 years were made by workers from the Mooseheart laboratory. For a

period of two weeks a worker recorded the number of servings eaten at a meal by each of the six or seven children sitting at a table, and also noted the children who seemed to him to be very good or very poor eaters. In order to rule out temporary disturbances of appetite, the observations were repeated by another observer after a period of several months, the children being regrouped at the tables so that comparisons were not made between the same six or seven children as before. Each group was made up of children of about the same age. Where the record of food intake and the observer's opinion both indicated that the child was a poor eater, he was classed in the anorexic group. The anorexic group were slender and more or less underweight for their height and age. The children who were good eaters during the two observation periods were designated the non-anorexic group.

Using the method described by Carlson (1916), records of the motility of the empty stomach were made on 18 children, 6 from the anorexic group and 12 from those who had been found to have good or hearty appetites. On some of these children the test not only included a period of gastric activity, but also the following period of relative rest and the beginning of a second period of gastric activity. At least five tests were completed on each child without disturbance in the form of colds, restlessness, etc. In some cases as many as 22 tests were made on one child.

RESULTS

(1) Prevalence of anorexia. Of the 200 children observed 13 (6.5%) had poor appetites as judged by their food intake and two observers' opinions of their appetite. Those showing very poor appetites were found to be from 10% to 22% underweight for their height and age by the Baldwin Wood tables. Children

Summary of Measurements

Measure	Anorexic Subjects				Non-Anorexic Subjects				Diff.	S. D. of Diff.	P.	Evaluation
	No. Subjects	No. Tests	Av.	S. D. of Distribution	No. Subjects	No. Tests	Av.	S. D. of Distribution				
1. Duration of activity period.	6	76	62.2 Mins.	23.55	11	150	74.6 Mins.	27.1	7.41	4.0	0.1 to 0.05	No significant difference between anorexic and non-anorexic subjects.
2. Height of large contractions.	6	73	2.5 Cms.	1.26	12	153	2.8 Cms.	1.51	0.279	0.025	Less than 0.01	Significantly higher contractions in non-anorexic subjects.
3. Number of contractions.	6	75	66.5	39.65	12	153	48.5	29.35	18.0	5.1	Less than 0.01	Significantly more contractions in anorexic subjects.
4. Duration of interval between periods.	3	27	35.2 Mins.	18.3	9	63	61.6 Mins.	23.85	26.4	4.6	Less than 0.01	Significantly shorter interval in anorexic subjects.
5. Duration of individual contractions.	4	42	38 Secs.		9	160	43 Secs.					Shorter duration in anorexic subjects.
6. Duration of incomplete tetany.	6	50	7 Mins.		12	93	7 Mins.					No difference between anorexic and non-anorexic.
7. Number of contractions in incomplete tetany.	6	49	16		12	93	16					No difference between anorexic and non-anorexic.
8. Duration of individual contractions in incomplete tetany.	6	49	26 Secs.		12	93	24 Secs.					No difference between anorexic and non-anorexic.

were not included in the anorexic group when their lack of appetite was associated with recovery from a severe illness or similar physical disturbance. Medical records on the group whose gastric motility was studied showed similar slight disorders in both the anorexic and non-anorexic children during the previous two or three years. No diseased condition which might explain the anorexia was found by the resident physician, who had cared for them since their entrance into Mooseheart.

(2) Analysis of the records.

In order to obtain as complete information as possible, a number of different measurements were made of the records of gastric activity, including the duration of the activity period, the number of large contractions in the period, the duration and height of individual contractions, and the length of the interval between activity periods. An activity period was measured from the time contractions of 1.0 cm. or more in height began to appear. These measurements were made because it was found that simple inspection or brief measurement of the records did not give reliable information for comparison of the anorexic and non-anorexic groups.

The initial treatment of the data by the computation of averages and ranges showed no marked difference which would clearly differentiate the anorexic from the non-anorexic group, because of the variability of individuals and the overlapping of groups. Newer small sample methods (Fisher, 1930) were used to determine definitely whether any significant differences existed between the two groups. By so doing it then became possible to state the following positive conclusions: The anorexic group had on the average a significantly shorter interval between activity periods and a greater number of contractions in a single period than the control group, both of these measures indicating greater gastric activity on the part of the anorexic children than the non-anorexic children. However, their contractions were found to be on the average shallower than those of the non-anorexic children which indicates that the gastric activity of the anorexic children was less vigorous than that of the control group. In line with this fact is the observation that individual contractions were of shorter duration in the anorexic children than in the non-anorexic children. No difference between the two groups was found in the durations of their activity periods, and in certain measures of the incomplete tetany periods.

If it is assumed that the vigor of individual contractions is the stimulating factor in hunger, the anorexic children with their less vigorous contractions may be thought to have less vigorous hunger feelings. The three different types of explanation of anorexia put forward in the introduction may hold in different types of cases. In cases studied in this paper it is felt that the factor of over-solicitude on the part of adults resulting in poor eating habits was not a factor, as there were seldom more than 2 or 3 adults to 16

children and opportunities for attention were limited. As regards the interfering sensations reported by some authors studying adult patients, the possibility of discomfort and distention on taking food has not been ruled out in the cases observed in this study. In many cases the children with small appetites would eat half a dozen mouthfuls readily, then slowly finish a small meal. It is possible either that unpleasant sensations occurred on slight distention of the stomach, or that with the presence of a small amount of food in the stomach, hunger feelings quickly disappeared. A study of gastric activity and sensations on taking small amounts of food would have been interesting in this respect. In regard to a possible association between the condition of anorexia and a frail type of body build, it was found that the children studied were slender and tended to be underweight. Some children of this body type had good appetites however. It cannot be said what part inheritance played and what part temporary environmental (or growth) factors, including small food intake, played in determining the slender, underweight condition.

Variations from test to test and from one individual to another which occur in both groups, cannot be explained at present, but may be due to such factors as variation in diet and in amount of food intake, variation in amount of exercise, and similar factors. In general, as determined by Fisher's Z test for variance, individual differences were found to be significantly greater than differences between tests on the same individual.

SUMMARY

(1) Thirteen children in a group of 200 (6.5%) were found on observation to have low food intake and moderately or definitely poor appetites.

(2) Records of the hunger contractions showed that children in the anorexic group had a greater number of contractions, a shorter interval between activity periods, and the hunger contractions were less vigorous in height and duration than in children of a control group having good or hearty appetites.

(3) No differences between the two groups were found in the length of the activity periods, or in the length of the incomplete tetany periods or the number of contractions in an incomplete tetany period.

(4) Since the anorexic children are differentiated from the control group by having more rapid, less intense gastric contractions, it may be that their small appetites are due to the lack of hunger sensations. It is also possible that in the anorexic children, the already weak gastric activity is more easily inhibited on slight distention with food, with a resultant small food intake.

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Editorials

IS THE STOMACH AN ESSENTIAL ORGAN?

ONE of the peculiar features about the disturbances which follow the complete removal of the stomach is that these disturbances vary considerably in different animals. Following complete gastrectomy adult dogs show only a mild and temporary anemia of the microcytic hypochromic variety (1). However, a more severe anemia may be precipitated by infection, prolonged diarrhea, pregnancy, or an inadequate diet. It has been shown that gastrectomized dogs are deficient in their ability to regenerate hemoglobin, a deficiency which responds to the giving of iron, but not of liver (2).

When fed a suitable diet gastrectomized dogs maintain their weight, and they may even gain, and they may live out a normal span of life. Such animals show slight rarefaction of the bones, but do not develop degenerative changes in the spinal cord (3). It has not yet been possible to duplicate these results with rats (4). This animal, when gastrectomized, exhibits impairment of nutrition, as reflected in its failure to regain the preoperative weight. A persistent microcytic hypochromic anemia is present, which responds incompletely to the administration of iron. No evidences of cord degeneration have been found, although the bone marrow shows hypoplasia. In the monkey the symptoms of gastrectomy resemble closely those found in the dog (5), whereas in the pig they are much the same as in the rat (6).

These differences may represent true "species differences" in the function of the stomach, or on the other hand, they may merely reflect the degree of success that has been met with in the search for adequate diets for the various species of gastrectomized animals.

Early experience in Dr. Ivy's laboratory with gastrectomized animals emphasized the importance of diet, and in view of this fact dietary factors should be carefully considered before trying to explain differences in behavior after gastrectomy by "species differences." Dietary factors may also account for the differences reported by various investigators in the effects of gastrectomy in animals of one species but different ages. Bussabarger, Freeman and Ivy (7) have reported that gastrectomized "puppies" develop osteoporosis of such severity as to lead to gross deformities of the extremities and to pathological fractures. This condition is ameliorated but not completely corrected by the administration of soluble calcium salts. Petri, Norgaard and Bing (8) reported that their gastrectomized puppies showed marked changes in nutrition and gait, as well as changes in the skin and nervous system. The differences in nu-

tritional state presumably resulting from the diets employed perhaps accounts for the differences in symptoms observed by these workers and by Bussabarger and his co-workers.

The experimental work with gastrectomized animals shows that the stomach cannot be considered an essential organ in the strict sense of the word. However, the stomach is more important in the economy of the growing than in that of the adult organism. It is more important also in the pregnant female than in the male. Proper nutritional care is indispensable in maintaining health in animals without a stomach and probably also in men and women similarly handicapped.

John S. Gray.

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GEORG WOLF

GEORG WOLF died on October 9, 1938, in Berlin, in his sixty-fifth year. He attempted over a period of twenty-five years to provide the medical profession with a safe gastroscope, and he saw his endeavor crowned with success when in 1932 the flexible Wolf-Schindler gastroscope was perfected. Therefore, in my opinion his name belongs with those who have made medical progress in this century, and the medical profession owes him homage.

Georg Wolf started as an employee in the electro-optical department of the large factory of Reiniger Gebbert and Schall in Erlangen where he gained experience in the construction of cystoscopes. Eventually, his sense of independence led him to the opening of his own establishment, located in Berlin between the buildings of the Charité and the large University Clinics in the Ziegelstrasse. There are the best cystoscopes, and other lighted tubes were manufactured.

The first step in the production of a gastroscope was taken in 1911 with the construction of the "flexible" Sussmann instrument. In this work Wolf showed an unusual ability to solve the most complicated mechanical problems. Even yet this instrument with its complicated straightening system, its many screws and levers, and its rotating objective appeals to us as a masterpiece of mechanical ingenuity. However, it became clear to Wolf that the best maker of medical instruments is helpless if he hasn't counsel from the

man who is going to use the apparatus. The Sussman gastroscope proved to be unusable because the conceptions upon which its construction had been based were wrong. After this disappointing experience Wolf became cautious in the choice of his medical collaborators, and he accepted new suggestions only when long preparatory work led him to believe that they were sound. He produced instruments incorporating minor modifications, such as the gastroscopes of Huebner, Hohlweg and Elsner, but only twice did he dare to make a big innovation.

When Hoffmann had shown in 1911 that theoretically it might be possible to look along changing curves Wolf made a gastroscope the tip of which was constructed according to Hoffmann's ideas. This tip could be bent forward and backward through an angle of 180° without interfering with the sharpness of the picture seen at the eye piece. But the instrument was clumsy; it had serious disadvantages and it was never put on the market.

After the construction of my first gastroscope in 1922 it was several years before I came in close contact with Wolf, but after that he decided to collaborate with me. His confidence in my suggestions was great, and I had to be careful in my letters for fear that he might carry out minor suggestions without delay. When he built the first flexible gastroscope he was so enthusiastic about it as a mechanical triumph that it took me a long time to convince him that it was not practical and that absolute flexibility was not desirable. What I wanted was some stiffness and elasticity and, in the upper portion of the tube, rigidity. In the five years from 1928 to 1932, Wolf made six different gastroscopes. Eventually he followed my advice and produced the beautiful instrument of 1932, the one which has made gastroscopy a safe and practical diagnostic method.

Georg Wolf lived long enough to see the triumph of our instrument throughout the civilized world. Until the end of his days he kept working on improvements and additions. He was the soul of his factory. In the last decades he had no real competitors in his field. He was a quiet, heavy man, with narrow, extremely sharp looking eyes. His home life was happy, and he was agreeably sentimental. He spoke with a "Berliner" accent and was a true child of this metropolis, the inhabitants of which so often excel by their cleverness and indefatigable industry. His collaborators and friends will not forget his personality, and gastroenterologists must never forget his name.

Rudolf Schindler.

THE DEATH OF PROFESSOR BOAS

SIR ARTHUR HURST, in writing to the British Medical Journal (1:1184, 1938) commented on the fact that Professor Boas, who was one of the founders of gastro-enterology, died in Vienna, March 15, 1938, at the age of eighty. He began his career as an assistant to Professor Ewald at the Augusta Hospital in Berlin in 1885. Working with Ewald, he devised the test breakfast which is so well-known to us all today.

Boas was a brilliant clinician and had the reputation of being the foremost gastro-enterologist of Europe. His textbook, "Diseases of the Stomach and Intestines" was popular for years, and it passed through many editions. It was translated also into several

languages. We owe to Boas the method of watching the stools for occult blood in diseases of the stomach and bowel. In 1898 Boas founded the "Archiv für Verdauungskrankheiten" and in 1920 he founded the German Gastro-enterological Society.

With the advent of National Socialism, Boas had to leave Germany and was fortunate to receive an invitation to continue his work in Vienna. When Vienna was taken over by the Nazis, Boas realized that the end of his working life had come. Having no desire to submit to further persecution and impoverishment, he took an overdose of veronal.

W. C. Alvarez, Rochester.

A LOCALIZED PATCH OF GONORRHEAL PERITONITIS WITH SYMPTOMS SUGGESTING ACUTE CHOLECYSTITIS OR APPENDICITIS

ONE of the rarer causes of acute abdominal pain is a patch of localized peritonitis due to invasion by the gonococcus. Doubtless in many of these cases the appendix is removed, and unless the surgeon immediately faces the fact that this organ looks fairly normal, and makes a careful and extended exploration of the abdomen, the real cause of the pain and tenderness and abdominal rigidity is not found.

In a recent article, S. J. Sullivan (J. A. M. A., 110: 1342, 1938) reported a remarkable case in which the surgeon operated on a married woman of forty-four who was seen with typical symptoms and signs of acute appendicitis and a white count of nearly 21,000 cells. At operation an acute suppurative appendicitis was found, but in addition there were slightly inflamed tubes, many petechial hemorrhagic areas along the last ten feet of ileum, and a little free fluid in the abdominal cavity. When cultures showed gonococci, the husband confessed that he was just coming down with gonorrhea contracted seven days before the operation. *Four days* before the operation he had had one act of intercourse with his wife. Since the wife maintained that she had had no other sexual contact, one must assume that gonococci were able to pass from the vagina into the peritoneum and produce an acute virulent infection *within four days*.

W. C. Alvarez, Rochester.

ERROR

In Prof. B. P. Babkin's Editorial in the January issue entitled "Testing of the Secretory Activity of the Gastric Glands in Man by Means of Histamine and Insulin" the figures for the experiment of April 29 were erroneously printed in the experiment of May 3, and vice versa. These columns should appear as follows:

April 29	May 3
5 units	0.5 mg.
insulin	histamine
2.7	129
3¼	1½
53	139
107	146
27	0.4
50	—

Book Reviews

Le Systeme Nerveux Vegetatif. By J. Tinel. Masson et Cie, Paris, 1937, 847 pages. Price 160 fr.

THIS is a monumental work on the vegetative nervous system. It covers 847 well-written pages in which few words are wasted. Seldom has the reviewer been more impressed by the way in which the field of science has been widening than when he contemplated the size of this volume on but one part of the nervous system of man. And even then it is not large enough, because when the reviewer looked closely at some of the chapters devoted to parts of the subject with which he is familiar, he was disappointed to find them so short and inadequate. Some of the inadequacy is due partly to the Frenchman's usual tendency to quote only from French authorities. A French writer seldom seems to know much of what's going on in the United States; he may know a little of what's going on in England, but if he knows of any good work coming out of Germany, he doesn't say much about it.

Actually, however, in view of the richness of the feast that is set before us in this book, it is hardly fair to cavil and to ask for more. An American would, of course, like to see some report of the large amount of work done on the medical side of the problem by George Brown, Adson and other Americans.

The book is well illustrated with 306 plates. Tinel starts out with an extensive description of the anatomy and histology of the vegetative nervous system. He then goes on to speak of the hormones that arise in this system, and the way in which the nerves respond to the administration of drugs. There are many chapters on the involuntary nerve supply of various organs and various parts of the body. Very curious are the photographs showing that nevi sometimes follow the segmental distribution of sympathetic nerves. There is much on the new and interesting subject of autonomic nerve centers in the diencephalon and the cortex.

There is much on the diseases and disturbing symptoms which are produced by abnormalities in the sympathetic nervous system, and this part of the book is perhaps the most nearly complete and the most valuable. It would doubtless well repay careful study. As is well known, the Frenchman is particularly happy and versatile when he is describing new syndromes.

It is probable that when more study has been made of these syndromes due to disturbances in the autonomic nervous system, more sympathy will be accorded many of the patients who are now looked upon as merely "neuros."

There is an interesting section on the causalgias, those miserable pains which persist even after all the known nerves to a part are sectioned. On page 617, Tinel speaks of cases in which pain not relieved by section of the nerve proximal to the lesion is relieved by section of the nerve distal to the lesion. This is a good sample of the puzzles which one encounters in this field.

There is much interesting material on the comparatively new science of studying autonomic reflexes. One can sometimes locate lesions by noting the behavior of pilomotor nerves, sweat glands, and even the erectile

tissue around the nipple. There is a discussion of the interesting problem of the nature of the sensory side of the autonomic system, and there is a final section on surgery and the use of drugs.

As the reviewer stated before, he wishes that Dr. Tinel had spent more effort in bringing the last section on surgery up-to-date. For instance, there is only a page and a half on resection of the presacral nerve, which is hardly enough space in which to discuss this often helpful operation, together with the indications for and against its use. Few references have been supplied. For a book of this size the author might well have supplied a bibliography of 700 titles. Actually, he gives less than two pages and a half to a bibliography in which he lists only a few outstanding articles. On the whole, however, one must compliment Dr. Tinel on the completion of a tremendous task, and one must thank him for bringing together in one place such an enormous amount of information.

W. C. Alvarez, Rochester, Minn.

The Horse and Buggy Doctor. By Arthur E. Hertzler. Harper and Brothers, New York, 1938, 322 pages. Price \$2.75.

WHEN a poor farmer's boy works his way through college and makes of himself a good physician, that is not news; it has been done too many times before. When a young doctor works day and night, covering a big territory in a horse and buggy and serving devotedly a large community, again, that is not news. When the young physician soon saves enough from a poor type of practice to take his family to Europe and spend two years making himself an accomplished anatomist and pathologist, his behavior becomes worthy of comment, and when in his later years he writes a delightful book of memoirs which is promptly chosen by the Book of the Month Club, his doings become decidedly newsworthy.

Actually, every physician, and particularly every physician past fifty years of age who has done general practice in the country, will delight in this book, which presents a picture of that heroic type of practice which was common before the advent of the automobile, the concrete highway and the hospital. It is the picture of a doctor driving long distances across the prairies by day and by night, in all sorts of weather, in rain storms and blizzards. Often at the end of a long journey there was no one to greet the doctor or let him in to warm his frozen hands, because the patient, some psychopathic woman, had gotten over her hysterics and gone to sleep. And then the poor doctor had to drive the long weary way home without a cent because "he hadn't rendered any service." But again there often was a patient with an intestinal obstruction or an acute appendicitis or an empyema, and then the operation had to be performed on the kitchen table, perhaps by lantern light and with the hired man giving the anesthetic. For years Hertzler kept his promise to his father that he would answer every call even when it came from those who couldn't or wouldn't pay.

Hertzler tells the story of the building of his first little hospital with the bitter jealousies and enmities which it aroused. After years of struggle and expense he was glad to give the place away for one dollar. His big reward was the knowledge that he had built an institution of great value to the community.

All through the book one finds much homely wisdom and much about the psychology of medical practice and the folly of trying to cure with medicine or surgery disease that is due to dissatisfaction, frustration, sexual starvation and unhappiness. The world has been made a better place by the work of men like Hertzler with their rugged honesty, good "horse sense," dry humor, and devotion to the service of their fellow men.

If in these changing times the medical profession had hunted for a public relations counsel to build up among the lay men and women of America a better appreciation of the type of public service rendered by the old-fashioned type of physician, it could hardly have found a better man than Dr. Hertzler. I doubt if any layman, no matter how bitter he might feel toward the medical profession because of some unfortunate happening, could read this book without concluding as Robert Louis Stevenson did, that the physician tends to stand above the common herd—a man of courage, devotion, honesty, ability and resourcefulness; one who thinks first of service to his fellow man and only secondarily of his pay.

The reviewer has only one sorrow in regard to this book, and that is that his father who, like Hertzler, sometimes swam rivers in flood and often had to trust to his old horse to find the way through storm and darkness, didn't live to read this Odyssey. How he would have loved it!

Walter C. Alvarez, Rochester, Minn.

Clinics on Secondary Gastro-Intestinal Disorders: Reciprocal Relationships. By Julius Friedenwald, Theodore Morrison and Samuel Morrison. William Wood & Company, 251 pages, 1938.

THIS volume undertakes to elucidate, for the medical and the general practitioner, the reciprocal relationship between organic diseases of the alimentary tract, with distant visceral manifestations, as well as the relationship between organic diseases of other viscera with associated predominant gastro-intestinal symptomatology.

The preface which states that "no such text is available in English" is hardly correct, for many classical and scientific papers and monographs have discussed such dual relationships as coronary artery disease with essentially only abdominal symptoms; renal calculus with gastric manifestations; tabes dorsalis with only alimentary disturbances. And who today is unfamiliar with the "gastric mask" of gall bladder disease?

Yet, though the subject is amply discussed in chapters of modern textbooks and in individual monographs, no one but the authors of this new book have attempted to correlate and collect the entire matter as a well-rounded and complete clinical treatise.

The gastro-enterologist knows well the confusion between the abdominal symptoms and underlying distal pathological disease. The medical student and the general practitioner are liable to have under-

estimated this reciprocal relationship and for them therefore, and for all of us, this volume is valuable.

The text is readable and fluid, the content treated in a direct clinical style and manner of the old masters. The literature is modern in the extreme, the periodicals have been combed for representative illustrations of points made. The style is good.

The newer statistical method of representing the incidence of disease and of portraying the frequency and order of certain symptoms is missing. The "business machine" method of presenting clinical facts is apparent nowhere in this volume. Old-fashioned clinical description is relied upon and case histories dot the book and clearly illustrate the bed-side observations made.

Very few adverse criticisms of the volume can be made. We would wish for a more outspoken opinion on the subject of chronic appendicitis. There should no longer be a need for straddling the fence and apologizing for those who hold to the existence of this flimsy diagnosis. Gastritis is again a bit loosely handled, particularly with reference to chronic nephritis, when actually the existence of chronic gastritis as a clinical condition needs much more evaluation.

The chapters on the endocrines and their relationship to gastro-intestinal symptoms are well put, nor is the value of endocrine therapy given undue prominence or mistakenly overestimated. In fact, throughout, the therapy is rational and sound and never overstated.

One regrets again the somewhat old-fashioned treatment of the subject of the so-called gastric neuroses. While the psychic approach is truly well-registered, one sees the hand of the old-time experienced clinician in such terms as "gastralgia nervosa," "hydrochlorhydria" (a term no longer tenable), "gastro-intestinal neurasthenia," etc. Unfortunately, the newer psycho-analytic, or Freudian approach is quite missing and the recognition of such common complexes as the suppression neuroses, anxiety states, the hysterias and the substitution phenomena are insufficiently elucidated.

The volume is a good readable text that portrays vast clinical experience, sound judgment, and an extensive knowledge of the past and of very current literature. It is highly desirable literature for all those actively engaged in the study and the practice of internal medicine.

B. B. Crohn, New York.

Triumph Over Pain. By René Fülöp-Miller, translated by Eden and Cedar Paul. The Bobbs-Merrill Company, Indianapolis, New York; 407 pages.

RENÉ Fülöp-Miller has done a splendid piece of work based obviously on much research through rare journals and archives. There are some chapters on pain in general which physicians may want to skip, but they will not want to skip a single paragraph of the fascinating story of the discovery of what is perhaps man's best gift to man: a story of envy and bitter jealousy, of ruin for three out of four of the contenders for immortality, of disgraceful spinelessness on the part of the President of the United States, and of thanklessness on the part of the public.

Morton, the man whose genius and persistence unquestionably gave surgical anesthesia to the world, died broken hearted and almost out of his mind. He

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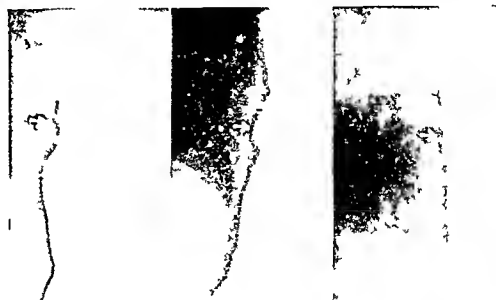
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Windwer and Matzner, *Am. Jl. Dig. Dis.*

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was importuned by creditors, and hounded to his death by the fiendishly clever and persistent persecutions of Jackson. Jackson, a chemist, doubtless gave Morton some helpful hints, but he didn't have the interest or courage to work out the problems of using ether, and when Morton went ahead, he, Jackson, so feared failure and trouble that he would have nothing to do with the project. Later, when Morton succeeded, Jackson claimed that he was the discoverer and that Morton was only his assistant. When this was disproved Jackson decided that if he couldn't have the credit, at least he'd see to it that Morton didn't get it, and with this spiteful motive, he spent the rest of his days hounding Morton and ruining him professionally, financially, and every way. Each time that Congress was about to give Morton an award, Jackson blocked it by hunting up the bringing forward as the "real discoverer" either Wells or Long, men who, it is true, had operated under anesthesia before 1846, but who had soon become so discouraged that they did not publish their work.

Eventually Jackson became so poisoned by his bitter thoughts that he went insane; Wells went insane and committed suicide in prison; Long died disappointed and unhappy, and Morton almost lost his reason. His death followed the shock of hearing that Jackson had broken into print again with new calumnies.

Doubtless the devoted admirers of Wells and Long will feel inclined to accuse Füllöp-Miller of bias, but anyone who with open mind will take the trouble to read the statements of Dr. Warren, to whom Morton went with his discovery, and of the other physicians at the Massachusetts General Hospital who saw the first operations done there under ether anesthesia will be satisfied that the man who gave anesthesia to the world was Morton. He it was who went on etherizing animals and breathing the drug himself day after day until he felt he could safely try surgical anesthesia in the hospital, and he it was who talked Dr. Warren into trying the new substance on patients. He it was who persisted until knowledge of the discovery spread over the civilized world.

Morton has been blamed by many for patenting his discovery and for trying to make some money out of it, but on examining the record, one is inclined to forgive him entirely. Almost from the start he granted to hospitals and to the medical department of the U. S. army and free use of the method. It is the American people who should feel ashamed because their government, after disregarding and infringing the patent it had granted to Morton, held up the compensation that was about to be granted him with the claim that since the patent had been infringed without contest, it had lost its value and was therefore not worth paying for! Actually, it appears that it was largely patriotism which, at the beginning of our war with Mexico, kept Morton from fighting for his rights. The pinch-penny arguments of the lawyers so impressed Pierce that he advised Morton to borrow the money to come to Washington and file a friendly suit against some government hospital. Then, with the title to the patent cleared, he, Pierce, would promptly sign the bill to remunerate Morton and right the wrong done him.

Unfortunately, when Morton reluctantly did as he was told, everything went wrong. The suit was contested, and everyone, including the medical profession, promptly began to hurl abuse at Morton. Pierce, ap-

parently without backbone or decency, let Morton down after getting him into the awful mess, and soon Morton found himself stripped by angry money-lenders, turned out of his home, and too ill and unhappy to work at his profession.

What a sorry story it is and how much wiser Morton would have been if he had invented a machine for killing and mangling young men, by the hundred thousand! Then he would have become a millionaire, and at his death a great mausoleum would have been built over his ashes.

Füllöp-Miller's book should be read by all research workers if only to serve as an awful warning to keep out of fights over priority of discovery. Let every man stick to his work; let him publish when he is sure of his results, and let him leave to posterity the decision as to who it is that deserves credit. Usually the world gives most credit, not to the man who saw dimly or saw first, but to the man who hammered away until he made everyone take notice of, believe in, and adopt and use the particular idea or invention. Often the world first ignores, then it ridicules, then it accepts. Finally there appear little men who, after much rummaging in libraries, come forth to prove that credit should be taken from the man who is being honored and given to someone long since dead.

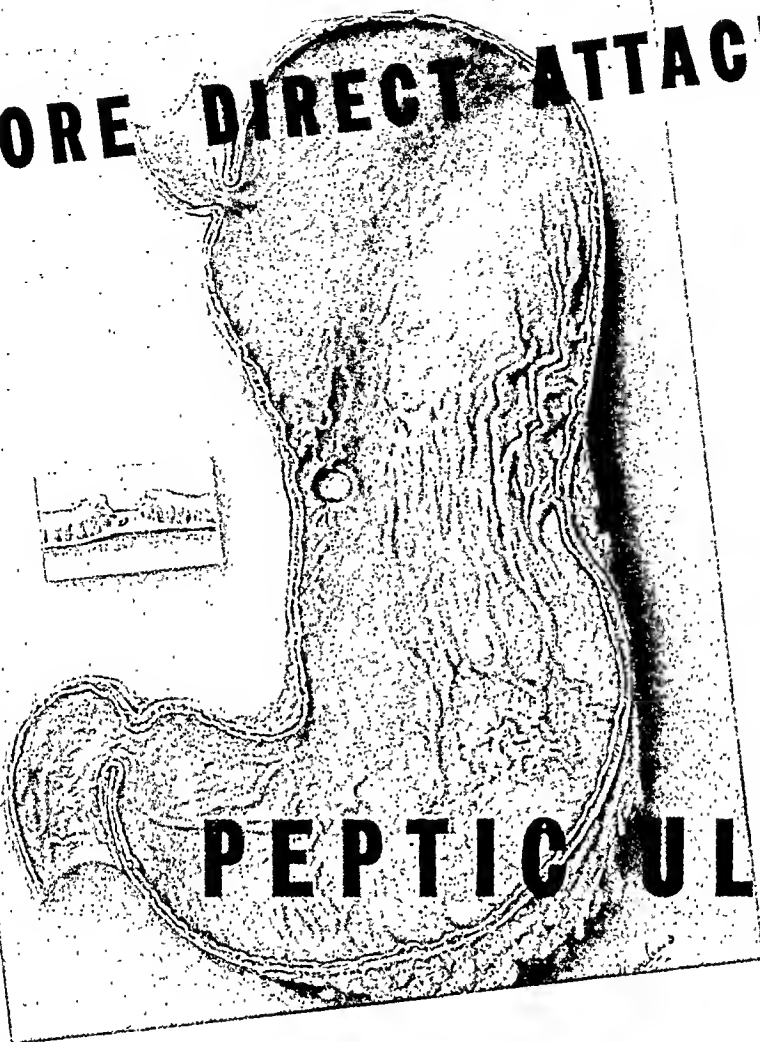
Der Magenkrebs. By Prof. Dr. Med. Georg Ernst Konjetzny, O.Ö. Professor der Chirurgie der Hansischen Universität, Direktor der Chirurgischen Universitätsklinik zu Hamburg. Cloth. Pages 286, including 155 illustrations, 20 tables, and an extensive bibliography. Stuttgart: Ferdinand Enke, 1938.

IN this monograph Konjetzny summarizes thirty years of study of the problem of gastric carcinoma. His earlier work is well known and has thoroughly established his position as one of the foremost authorities on the subject. The present monograph reaffirms the views previously published, coordinates the data, adds much new material, and presents a complete picture of our present knowledge of the genesis of gastric carcinoma and its clinical application. The book will be welcomed by all those interested in the various aspects of the problem.

In the introduction the author calls attention to the well-known fact that the stomach is the organ most frequently affected by carcinoma and that today the majority of the patients so afflicted come to the internist and the surgeon too late for cure. In the battle against gastric carcinoma only two possibilities exist: Prophylaxis or early radical surgical treatment.

Under the heading of etiology Konjetzny discusses first the role of heredity and concludes that cancer as such is not inherited, only a certain tendency or organ disposition. External conditions are thought to be the more important factors. The theory of contagiousness and infectivity seems disproved, as does the Cohnheim concept of carcinoma arising from embryonal cells left over after the development of the fetus and its organs. Trauma is considered significant only as it relates to the sequelae of corrosion of the mucosa, as in acid or alkali poisoning. Virchow's theory of carcinoma as a resultant of local disease processes is accepted, and a large section of the monograph is devoted to the thesis that "the chronic inflammatory conditions which demand greatest consideration as the basis of gastric

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carcinoma formation are: The chronic gastritis with its sequelae and the chronic gastric ulcer." Konjetzny's life work indeed has been the study of the relationship between chronic gastritis, benign ulcer, and carcinoma. He views gastritis as the basis for both ulcer and carcinoma. In his experience gastric carcinoma is always associated with a pronounced chronic atrophic or atrophic-hyperplastic gastritis. Carcinoma never develops in a normal gastric mucosa. The essential process in the gastritis-carcinoma relationship is not the inflammation but regenerative changes in the epithelium constantly induced by it. The complete transition from pure gastritic changes to polyp formation and carcinoma is described in detail and well documented with convincing illustrations. The carcinomatous development begins in the cells over a broad area of the mucosa and hence is multicentric in origin. The subject of carcinomatous transformation of a benign ulcer is discussed at length. The conclusion is reached that it is not possible by clinical methods alone to make such a diagnosis. Pathologic evidence, especially the histologic, is more definite, but here also difficulties exist. The diagnosis cannot be made on the basis of any single pathognomonic finding but rather by a careful analysis of all the evidence. Carcinoma may develop in the edge of a benign ulcer or adjacent to the ulcer but independent of it, related not to the ulcer but to the gastritis, to which Konjetzny attributes both the ulcer and the carcinoma. With regard to the differentiation of ulcer-gastritis and carcinoma-gastritis Konjetzny says that in ulcer the gastritis is usually more acute and localized to the antrum whereas in carcinoma the gastritis tends to be more chronic and to involve larger areas of the gastric mucosa. There is, however, no specific or fundamental difference.

Among the macroscopic forms of carcinoma Konjetzny distinguishes the following types:

1. The pronounced mushroom or polypoid tumor developing chiefly into the lumen of the stomach.
2. The ulcerated dish-like growth with clearly defined borders.
3. The ulcerated carcinoma without a definite wall or a sharp border and with infiltration of the gastric wall beyond the edge of the ulcer.
4. The definitely diffuse type with gradually decreasing thickness of the gastric wall from pylorus to cardia, the borders of the tumor not being definitely palpable, or with thickening of the entire gastric wall.

The histologic types are variable and are not to be correlated with the macroscopic. The prognosis for surgical treatment is, on the whole, much better in the first and second groups than it is in the third and fourth. A histologic classification is not of much prognostic value.

Effective therapy depends first, upon early examination and second, upon gastric resection of all early carcinomas and indeed of all cases of polypoid gastritis, this being definitely a precarcinomatous, if not already carcinomatous, condition. All patients with digestive symptoms should report promptly to the physician, who should use all available diagnostic means necessary for the establishment of a definite diagnosis. The history, physical examination, and the gastric analysis are not sufficient but should be combined with a search for occult blood in the stool and with careful roentgenologic and gastroscopic examination. These methods are most valuable. The author

is opposed to exploratory laparotomy as a diagnostic procedure because the methods mentioned are reliable and also because small carcinomas often cannot be palpated even when the surgeon has the stomach in his hands. When a portion of the stomach is held in suspicion clinically, it should be resected. Resection should be carried out in almost all cases of carcinoma even though a very radical operation is required, such as complete gastrectomy or partial gastrectomy combined with partial colectomy. The chief contraindications to resection are *definite, proved*, distant metastases or extensive carcinomatous peritonitis. Significant palliative effects have been obtained even when Krukenberg tumors had to be removed in addition to the gastric lesion. In spite of the fact that Hitzberger and Markler found thirteen-year cures in only two per cent of 272 patients with gastric carcinoma, Konjetzny feels that undue pessimism is not warranted, even in the young. The longest cure observed in the Breslau Clinic was that of a man operated upon when thirty-one years old and followed for twenty-one years. With earlier diagnosis and earlier radical resection better results should be obtained.

Vitamin B₁ and its Use in Medicine. By Robert R. Williams and Tom Douglas Spies, N. Y., The Mac Millan Company, 411 pages, 1938.

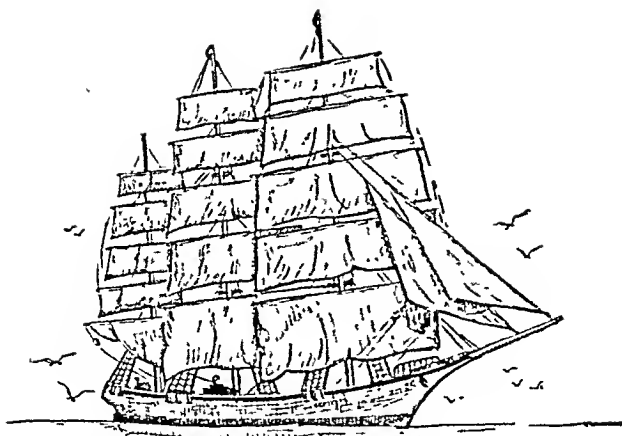
IN the past few years so many contributions to the subject of vitamins have accumulated that many physicians have expressed frankly their inability to keep "au courant." This has been true particularly in the case of Thiamin Chloride, (as Vitamin B₁ has been tentatively named). This book has been timely written and presented and will come as a welcome friend to those frantically striving to maintain their heads above the tidal wave of vitamin researches.

The authors have set as their goal the painstaking compilation of all known facts—as well as many unproven concepts—of this vitamin. The book has been written in two parts, of which the first part (120 pages) will interest the clinician mainly. Here he will find listed the many conditions in which Thiamin has been used. Often the material is presented in abstract form permitting the reader to exercise his own critical judgment but at times the authors express their own views. Thus in the chapter on prevention and treatment we read this statement—"Irrespective of predisposing conditions and co-existing diseases, the authors consider the manifestations of Vitamin B₁ deficiency as Beriberi."

This concept may prove startling to those physicians who view Beriberi as a distinct and often serious clinical entity. It may be difficult to reconcile this viewpoint with the clinical uses of this vitamin. However the authors are well aware that "the use of Vitamin B₁ in medicine" is in the process of evolution. Much will be modified even in the next few years.

Especially illuminating is the collection of data on the pathology and pathological physiology of Vitamin B₁ deficiency in animals and humans. In the short space of twenty-two pages is grouped an enormous amount of material culled from all types of scientific literature, literally from all parts of the world. Just to read this chapter alone is a saving of many hours of arduous library work.

Many tables of foods and diets and their B₁ content



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are given not only in part one (pp. 112-118) but also in part two (pp. 236-240). These will be of great value in modern dietetics as most if not all of the older tables contain many inaccuracies.

The inclusion of a short note on the toxicology of Vitamin B₁ will be appreciated by many clinicians who have repeatedly inquired about this problem. Death can be brought on by massive doses in the experimental animal and the authors express the therapeutic safety as follows—"The ratio of the effective therapeutic dose to the minimal toxic doses is between 1:7,200 to 1:36,000."

Part two contains the historical and experimental data. The busy practitioner may find little to guide him in his clinical problems, but the student of medicine and the chemist—and many others—will experience a real joy at the concise and yet complete collection of data about Vitamin B₁.

From this part of the book will come the stimulus to solve many of the remaining problems of Thiamin Chloride; the relation to thyroid activity; the role it plays in the function of the liver; the relation of thiamin and nicotinic acid to the carbohydrate metabolism, etc.

The authors are acutely aware of the fundamental nature of their work in this field. In an excellent recapitulation their keen insight is focused in well balanced statements in which enthusiasm and conservatism go hand in hand. Almost prophetic is their statement that "it seems likely that the Vitamin B₁ requirement of all living things will turn out to be essentially alike in terms of molecules of the metabolite which are converted into energy."

The authors may well be pleased. They have written a book which has been needed urgently by the medical profession. No one interested in Vitamin B₁ can do without it. Nowhere else can be found all of the present knowledge of Vitamin B₁.

Martin G. Vorhaus, New York City.

Food, Health and Income. By J. B. Orr. London, Macmillan and Company, 1937. Price \$1.00. (Second Edition).

EVERY student of mass dietetics will want to study this little volume, since it brings much of the information that is needed before men can decide just where to put the dividing line between a diet which maintains life and that which insures health, good growth, and optimum resistance to disease.

As Dr. Orr points out, conditions in England have been improving, but still half of the population must live on so small an income that it is doubtful if parents can properly feed their children. Actual tests have shown that an improvement in the diet of children of the poor will result in improved health and increased growth. The diet of 4,500,000 people in the United Kingdom appears to be deficient in every constituent examined. The 9,000,000 in the next higher economic group get enough protein but too small a supply of vitamins and minerals. Another 9,000,000 live on what appears to be a deficient diet.

Curiously, the consumption of bread and potatoes is about the same in the poorest and the richest homes. With increased income an increase is noted in the consumption of milk, eggs, fruit, vegetables, meat and fish. A decrease is found in the consumption of condensed milk and margarine.

Attaining Manhood. By George W. Corner. Harper & Brothers, New York, 1938, 67 pages.

MANY men and women have tried to write a little book to give instructions to children in matters of sex. Few could approach the problem with greater wisdom than that possessed by Doctor Corner. As everyone knows he is one of the world's ablest students of the anatomy and physiology of the reproductive processes in the body. He also has a fine command of the English language, and is one of America's authorities on the history of medicine. This little book was written primarily for the instruction of his own boy.

Naturally with Doctor Corner's training one would expect him to devote most of the book to an explanation of the anatomy of reproduction and the development of the ovum and the fetus. If there should be any later editions, Doctor Corner will probably add more material on the problems of sexual behavior. The book is sound, and it can be recommended to parents who want something to give to their children.

The Spivack Gastrostomy. By Frank H. Baehr, M.D. and Stanley Frehling, M.D., Westfield, Massachusetts.

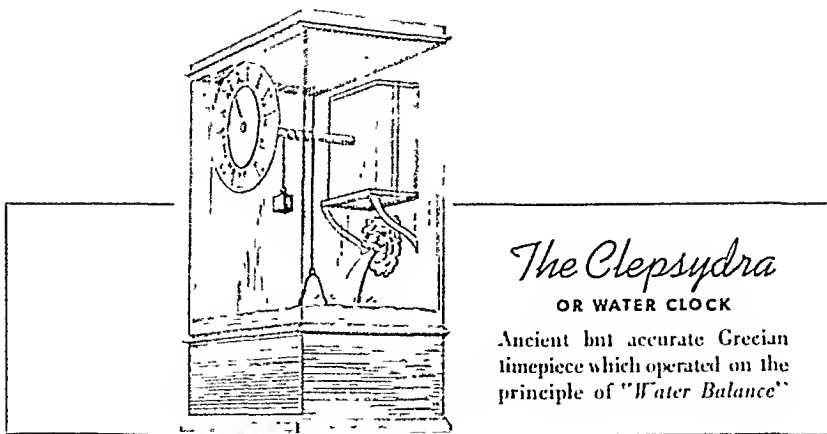
THE authors are extremely enthusiastic about the possibilities of this operative procedure. The article presents one case report where the technical result was satisfactory. The preparation of a tube made from a portion of the anterior gastric wall and brought out through the abdominal wall is ingenious. The concomitant formation of a valve-like structure at the junction of this tube and the stomach proper, acting so as to prevent the regurgitation and leakage which has been the greatest problem to the surgeon is important.

The paper itself has an excellent description of the operation and is accompanied by well-prepared and clear drawings of the entire procedure. Whether or not the procedure should be adopted more uniformly remains to be seen. The satisfactory gastrostomy has not as yet been perfected, and all avenues should be explored in an endeavor to obtain perfection.

Henry H. Lerner, New York, N. Y.

Cabot's Physical Diagnosis. By Cabot, Richard and F. Dennette Adams. 12th ed., Baltimore, Wm. Wood & Company, 1938, 846 pages.

THE thousands of physicians in this country who learned much of what they know about diagnosis from Cabot's book on the subject will welcome as an old and deeply respected friend this twelfth edition. The book has grown greatly in size and completeness since it was first issued in 1900. As Dr. Cabot says, during the earlier years it was a one-man book, based largely on his own experience, but now the field of medicine has become too great for any one man to be an expert in all specialties. Hence it is that in this edition Dr. Cabot has appealed for help to a large group of physicians, many of whom work with him at the Massachusetts General Hospital. The book has been entirely revised and rewritten. New illustrations have been used, and there is an increase of 50 per cent in the material without an increase in the price of the book.



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Mentality and Homosexuality. By Samuel Kahn. Boston, Meader Publishing Company, 249 pages. Price \$3.00.

EVERY so often the internist will run into a case in which a woman's nervousness proves to be due to the fact that her marriage is going on the rocks, and this because of the homosexuality of the husband. Commonly, the physician will not get the story, and then, of course, he will not be able to help the patient with her mucous colitis, her nervous breakdown, or her nervous regurgitation. But if he is sufficiently interested in the life tragedies of his patients to get the story, what is he to think and what advice is he to give?

To most normal men and women, the subject of homosexuality is so disgusting that they refuse to face it or to learn anything about it, and even the psychiatrist, the penologist and the police judge usually display woeful ignorance in regard to the problem.

The only way in which to learn about homosexuality is to study homosexual persons. No amount of theorizing will take the place of the information that can be gained through getting the confidence of these people and talking to them sympathetically about their problems. A man would have to be hard-hearted indeed not to sympathize with the sadness or horror which comes over some of these people when they discover that through some miserable prank of nature they are to be denied the greatest comfort that can come to a human being and that is to have a mate and home and children. To understand the tragedy of the situation, one need only read "The strange confession of Monsieur Mountcain," or "The Invert, by Anomaly," or a story called "Death comes on an Atoll," published in the *Atlantic Monthly* some three or four years ago.

One of the best places in which to meet many homosexuals and to get to know them well is a big penitentiary, and Dr. Kahn, who has been a prison physician and psychiatrist, has taken advantage of his opportunities to write an interesting and helpful book on these people and their problems. It is doubtful if any open-minded person can read this book without coming to the conclusion that these people are primarily to be pitied, and that they should not be hounded savagely by the law. Neither should our laws be so designed as to help the band of blackmailers who now prey on homosexual men in every large city.

Kahn shows that most of these people were born handicapped, in that they come from families in which there is much insanity and degeneracy. Although some of these people are gifted and able, especially in the field of art, many are of low mentality, and easily influenced by the suggestions of others. Because of this they are easily led astray by criminals, and taught bad habits such as the use of morphine and cocaine. Many doubtless take drugs to help in the forgetting of their sorrows.

The anthropologist and the collector of underworld argot will be much interested in the many special names which these people give to the various types of homosexual persons, both male and female. Many men know what a "fairy" is, but few could define a fag, a brilliant, a bulldiker, a red top, a fish, or a queer bird.

Very enlightening are the love letters which Kahn publishes. Having been sent from one homosexual prisoner to another, they show something of the psychology of these people. Obviously, their type of love

is just as vivid and compelling to them as is that of any heterosexual person to him or her.

This book should be in the library of every penologist and psychiatrist. It is to be hoped that some day we Americans will be sufficiently civilized so that our laws in regard to these people will either be taken off the books or else made more merciful. Today they are inspired by ignorance, savagery, dislike and abhorrence; some day they must be based on knowledge, and sympathy for the unfortunate. Once mentally unbalanced persons were chained up and treated like wild beasts; today most of them are cared for mercifully. About the only psychopaths who are still treated savagely are the paranoiacs who commit murder and the homosexual men. For some unknown reason, homosexual women are not annoyed by the law, although their numbers appear to be much greater than are the numbers of homosexual men. Perhaps women too would be treated brutally if women had made the laws.

Medico-legal Aspects of the Ruxton Case. By John Glaister and James Brash, Baltimore, William Wood & Company, 1937, 284 pages. Price \$6.00.

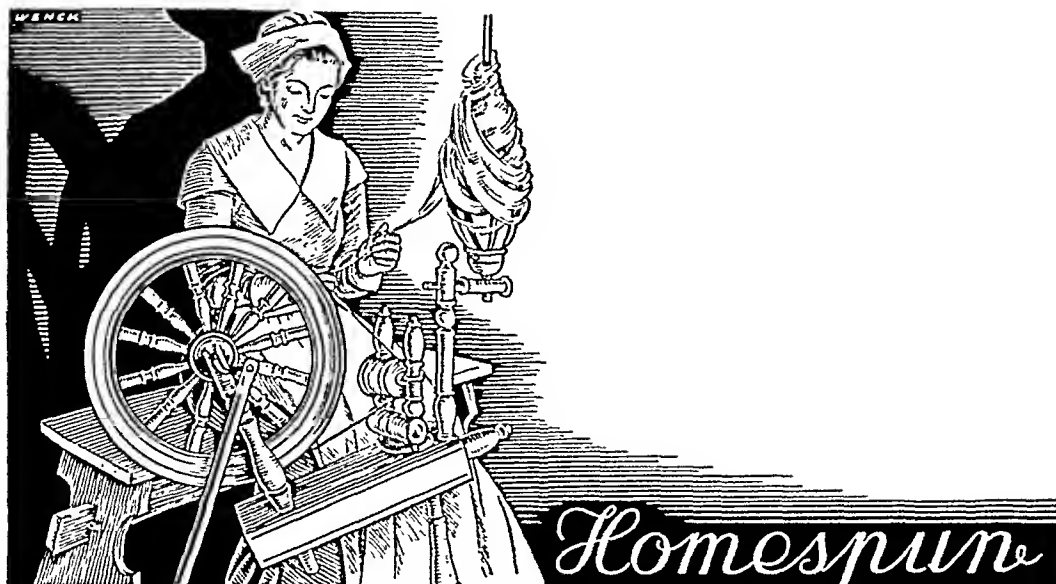
THIS is a most remarkable story of the work done by a group of physicians, anatomists, and other medical men at the University of Edinburgh in an effort to establish the identity of two bodies, so hacked to pieces and disfigured that no identification could possibly be made by relatives. The murderer was a physician who killed his wife and her maid. He then cut the bodies to pieces, removing muscle from bones, dissecting the skin off the face, and removing the fingers so as to get rid of the prints. He then threw the remains into a ravine some miles from the scene of the crime, and there they were found after a couple of weeks.

In order to produce a corpus delicti, anatomists put the scraps of the bodies together and established the fact that they belonged to two women. In each case they superimposed a photograph of the head and face over the skull and showed that the fit was good. They checked many details of teeth, of foot size, as compared with the victims' shoes, and so forth. They estimated the standing heights of the two bodies, and altogether, they did a tremendous amount of work, in which modern science played a great part. In the end they had no difficulty in convincing a jury that the mangled remains represented the bodies of the doctor's wife and the maid.

The book is well illustrated, and it doubtless will constitute for the next hundred years an invaluable text for all medico-legal workers. Although not particularly gastro-enterologic in its interest, it will be of great interest to physicians in every specialty, and to all those who are interested in the behavior of the psychopath and the murderer when he happens to be a physician. There is a good summary of similar famous cases in medico legal literature.

Anal Fissure, an Evaluation of Treatment with Oil Injections. By George S. Speare, M.D. and Roy E. Mabrey, M.D., Boston.

COMMENCING with a clear concise description of the anatomy of the anal canal, the article goes on to discuss the etiology of fissures. The authors state that fissures are the result of infections of abnormally



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deep crypts with resultant ulceration of the crypt wall or its tearing by the passage of hard feces. There are two possible results of an infected crypt. If the lumen of the crypt is directed downward along the wall of the anal canal between the mucosa and the sphincter, a fissure is formed. On the other hand, if the lumen of the crypt is directed away from the anal canal toward the fibres of the internal sphincter, the infection breaks through into the tissues of the ischio-rectal fossa and forms a peri-anal abscess resulting in an anal fistula.

The symptom complex of anal fissure consists of pain, marked at the time of bowel movement with occasional bleeding, itching, constipation, anal discharge, the presence of a lump, tightness of the sphincter and tenesmus.

The paper concerns itself with a report of 129 patients, 76 of whom were treated before the introduction of the oil treatment and 53 with the oil injection treatment. The method of injection and the solutions used are described. The end result in both series of cases, although not striking, shows a greater percentage of relief by the use of oil injection than by other treatments. In the cases that were operated on, however, a larger percentage of cures was obtained. Nevertheless, the authors feel that the oil injection treatment is of importance in the treatment of well-established chronic cases, obtaining between 40 and 60 per cent cures in these cases which previously could only be cured by surgery. The avoidance of hospitalization, they maintain, justifies the preliminary use of this method as against operation which could be performed later if the oil injection treatment failed.

Henry H. Lerner, New York, N. Y.

High blood pressure and longevity, and other essays selected from the published writings of David Riesman, M.D., Sc.D., LL.D., Chicago, Philadelphia and Toronto. John C. Winston Co., 1937, 726 pages. Privately printed.

EVERYONE who knows Dr. Riesman either personally or from his writings will be interested in this book, which reveals many of his keen observations and much of his fine philosophy. As would be expected of Dr. Riesman, the essays are written in simple, beautiful English, English that can be read with pleasure. As one would expect also of a wise clinician, Riesman emphasizes that which is so much needed today, namely, the use of the eyes and ears and fingers, the taking of an accurate and adequate history, and the making of a real physical examination. Finally, some cerebration must go into the matter of following clues and deciding what is the most likely lesion to account for the clinical picture as a whole. Riesman knows full well how to use the new methods of diagnosis, but he knows the folly of trying to make diagnoses through them alone, without the help of any cerebration.

Although the title of Riesman's book gives the impression that the articles are mainly on high blood pressure and longevity, actually they deal with all sorts of interesting subjects of decided interest to gastro-enterologists, and in fact, every gastro-enterologist should make a point of reading the article on the taking of a good history. It is packed with valuable information. The article on the recognition of

failing heart by the gastro-enterologist is also very valuable and worth rereading by every clinician in the country. There are a number of delightful essays on the history of medicine and on primitive man. This book would make a fine present for any young man starting out in medicine.

A Bibliography of the Works of Ambroise Paré. By Janet Doe. Premier Chirurgien et Conseiller Du Roy. Chicago, The University of Chicago Press, 1937. Price \$5.00.

THE life and writings of Ambroise Paré, one of the fathers of surgery, one of the most interesting of men, and certainly one of the most interesting of physicians of whom we have record, are well worth studying. Originally a simple barber-surgeon, without learning, he rose by his own efforts to be the ablest surgeon of his time, an able writer, and the companion and friend of kings. For many years his teachings and writings had a tremendous effect on the practice and thought of physicians the world over. To show how far this influence went one need only remark that in the seventeenth century, two hundred years before Perry came to open the ports of the Mikado to foreigners, Paré's great opus was translated into Japanese.

Paré wrote not only on surgery but on anatomy, gout, plague, poisons, obstetrics, monsters, natural history, mummies, pathology, travel and poetry. When writing from his own experience he was forthright and sensible, modern in his scientific outlook, and in advance of the other writers of his time.

Every bibliophile and student of medical history is now indebted to Miss Doe for a beautiful piece of research, during the progress of which she had to ransack the public and private libraries of the world. Every lover of medical books will want a copy of this volume. It is well illustrated, and with all its lucid comments, it constitutes practically a Life of Paré.

A Textbook of Biochemistry. By Roger J. Williams. First Edition, 439 pages, 17 figures, 40 tables. Published by D. Van Nostrand Company, Inc., New York City, 1938.

THE author of this new text indicates as one of his main objectives the development of insight on the part of the student. The selection of material, he states, has been made with this purpose in mind. Whether this objective has been realized to the satisfaction of the majority of teachers and students will only be revealed by the extent to which this text is used in teaching. It seems likely that in many cases a somewhat more detailed presentation will be preferred. The usefulness of this volume for reference purposes, at least, would appear to have been impaired by condensation and elimination. Also certain recent developments which might logically have been included are not discussed.

The author's style is pleasant and readable, and the emphasis and clarity with which the more important aspects of his subject are treated will undoubtedly appeal to many teachers. It may be useful to the clinician who wishes to have a readable review rather than a text for reference on phases of biochemistry which are not of major importance.

Lathan A. Crandall, Jr. Chicago, Illinois.

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A truism that is always worthy of attention is the fact that we take too much for granted and know too little about many of the common things of life.

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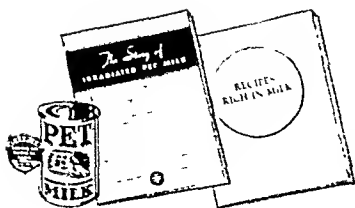
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Non Ulcerative Disease of the Duodenum. By I. Pavel et A. Pauneseo-Podeano. A volume of 204 pages with 57 illustrations. Masson and Co., Editors, Paris.

The history of the duodenum has been so far mainly concerned with the ulcers and its complications, but the authors claim that the other aspects of the duodenum pathology are worthy of an extensive study. For instance, they write that both the pseudo-ulcerative and hemorrhagic types of chronic duodenitis are bound to receive more and more attention in general practice. These conclusions were reached in the course of various researches devoted to some nearly

segment of the digestive tract. The first chapter contains a detailed analysis of the most recent conceptions regarding the duodenal physiology and bacteriology. About the much discussed and varied action of "secretion," normally present in the mucous membrane of the small intestine. They suggest that only the stimulation of liver and pancreas to secretory activity and favorable action on diuresis should be considered as definitely proved. For those interested mostly in the bacteriological point of view, we shall add that not only is the duodenum usually sterile in the normal individual but also that experimental introduction of

germs within its lumen cause positively no damage, because most of the invaders are instantly killed.

This chapter ends by a review of the normal duodenal motility as controlled mostly by X-rays and experimental surgery.

Duodenitis as a clinical entity has been, up to now, according to P. and P.P. only a so-called "residual diagnosis." Every possible affection was brought in mind before duodenitis could be admitted. The patient suffering from duodenitis may be seen with a clinical picture of 1o.—common duodenal ulcer; 2o.—with hemorrhagic symptom; 3o.—with jaundice.

a.—*The common pseudo-ulcerative type.*

Its clinical description so perfectly simulated that of gastric and duodenal ulcer or cholecystitis that roentgenology is primary necessity in arriving at the correct diagnosis. Kirklin has classified in the following order the X-ray findings in duodenitis:

a.—exaggerated irritability of the duodenum, barely allowing visualization on account of the faster transit; b.—reticular aspect of the relief of the mucosa; c.—absence of the typical "niche" of ulcer; d.—absence of gastric retention in non-complicated duodenitis.

Etiology and pathogenesis have shown the frequent association of duodenitis with the gastritis of nervous or heavy drinking patients. Cholecystitis and even appendicitis have also been found in connection with it.

b.—*Hemorrhagic type.*

This monosymptomatic form has also been linked with cholecystitis in 10% of the cases and especially with chronic infection of the ileo-cecal portion. Experimentation has proved, beyond doubts the eagerness shown by the pyloro-duodenal segment in answering by an active and very often hemorrhagic congestion to irritating processes started from any point of the intestinal tract, and from the cecum and appendix, in particular. These facts have been certified in the course of surgical procedures which is also the only way of reaching a correct differential diagnosis.

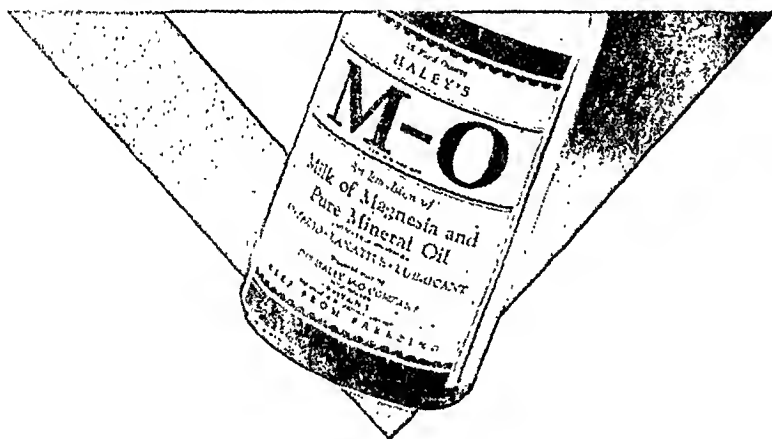
c.—*Duodenitis with jaundice.*

This type was quite familiar to the medical world of the last century and gradually dropped out of the picture before 1900. The recent introduction of Lyon-Meltzer test in daily clinical work and X-ray advancements have called upon a renewal of the importance of that form of duodenitis which can be thus classified:

1o.—Chronic duodenitis with prolonged jaundice; 2o.—duodenitis in the course of catarrhal jaundice.

Chronic duodenitis with jaundice

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has the clinical picture of a prolonged catarrhal jaundice coupled with a very satisfactory state of health. A Lyon-Meltzer test, very often impossible on account of the spastic reaction of the duodenum, reveals characteristic cytology and bacteriology—along with positive X-ray findings of congestion and spasticity. Although careful studies have been carried out in many cases, it must still be stated that the disease remains of unknown etiology, pathogenesis and pathology. The Lyon-Meltzer test is the most effective treatment, surgical intervention must, however, be contemplated when jaundice has been lasting over two months.

Duodenitis and catarrhal jaundice. —Different workers in various fields of observation have been very positive about the existence of duodenitis in the course of catarrhal jaundice but radiologic advancement was needed to emphasize these notions. Hatzigano and Hanganotz have X-rayed twenty-four cases of catarrhal jaundice. In twenty cases, they found a disturbed duodenal evacuation, suggestive of atonic stasis. These authors were specially interested in the radiological aspect of the duodenal segment on the course of catarrhal jaundice, because they had been struck by the analogy between the clinical picture of the onset of catarrhal

jaundice and acute duodenal stasis and its secondary intoxication.

The next chapter is devoted to another conquest of roentgenology, diverticulosis of the duodenum. After discussing pathogenesis and pathology, the diversified clinical pictures and complications are studied at length, followed by a careful review of correct roentgenographic technique and proper interpretation of X-ray films. Surgical treatment must be brought forward as soon as dietetics and drugs have failed to relieve pains and prevent complications.

Duodenal stasis. This chapter is a survey of all affections characterized by a delayed emptying of the duodenum. Mechanical causes are expected to be found in most cases; for instance, an unusual flexure, some inside obstacle or a compression from the outside.

P. and P.P. insist on the fact that pathological and clinical findings are directly related to localization as much as to intensity of the stenosis. They draw a complete clinical picture of high intestinal occlusion, including the important blood reactions: high blood urea, acidosis, high alkali reserve, and hyperpolypeptidenia. The severe intoxication encountered in duodenal obstruction is the combined result of excessive loss of fluid, exaggerated toxin production within the walls and lumen of the duodenum and intensified absorption, very unusual in this high portion of the small intestine.

Special mention is made, afterwards, of (a) periduodenitis inflammatory and essential, with its rather deceptive nervous and mental perturbations, (b) compression by the mesenteric pedicle and specific "posture relief" in such a case, (c) and finally, post-operative or rather post-anesthetic duodenal occlusions with their dramatic symptoms and energetic treatment.

Functional stasis is also studied. It is either secondary to spastic duodenitis, or to general hypotonic duodenal reaction. Both ailments may be easily recognized by X-rays.

Belief comments are added, to end the book, about duodenal tumors, peculiar malformations, and parasitology. 57 illustrations, mostly films, very well chosen and expensive, are an important contribution to this up to date survey of duodenal pathology.

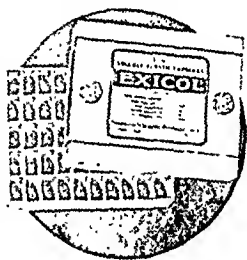
Roger Dufresne, Montreal.

Intoxication and Nutritional Deficiency. (Intoxications et Carences Alimentaires). By M. Loeper. 255 pages, Masson & Cie, Paris, 1938.

This publication may be considered a sort of "Medical Authority"—of Professor Loeper's teachings.

Each chapter is a contribution by a former pupil or assistant who under

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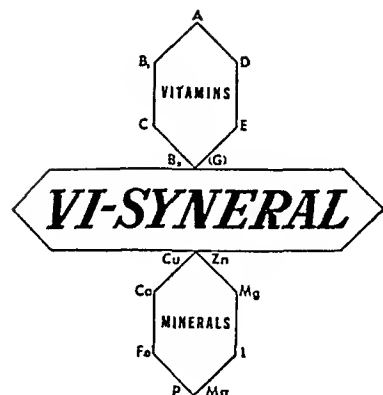
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*Amer. J. Digestive Diseases, Vol. 5, No. 6, p. 348, August, 1938.

**J. Lab. and Clin. Med., 19:567, 1934.

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1. Report of League of Nations Health Comm., Dec. 6, 1935

2. Eddy, Walter E. (Special research report on Vi-Syneral).

3. Privitera, A. T., Arch. of Ped., April, 1933.

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the instigation of their chief and teacher have been carrying out independent investigation on important problems pertaining to the pathogenesis, dietetic and treatment of nutritional disturbances in man.

These findings have been grouped in this volume with the hope of being of some use to the practitioner.

Much will be found which may on the surface appear only of didactic interest or may appeal to the biochemist, such as the chapters on Polypeptides and amino-acids; the biochemical changes brought about in the large and small bowel, due to variation of intestinal flora. On the other hand, broad views are taken of that complex pathology encountered

in that strange system, which goes to make up, the weakness, the hypersensitiveness and the protection phenomena (organization) of the alimentary tract. It teaches reasons for hypersensitivity and toxicity.

Loeper's personal contribution to this chapter is most inspiring, for it is the outcome of long years of teaching and research which have borne fruits at the bedside as well as in the laboratory.

The role played by histidine in the tissues. The tonic effect of the imidazol compounds reactions. The definite neurovascular changes as due to intestinal disturbances—as an important contribution by Garein.

One may also read with much inter-

est the "Defensive and Protective Factors" of the digestive tract.

A few chapters have been reserved to a study of the Detoxicating action of the liver, to which has been added some interesting research on Deficiency of Vitamin C in the liver. The second part of this volume is limited to a study of deficiency diseases, resulting from alimentary disturbances and chemical changes brought about by gastro-intestinal pathology.

The final chapter gives further treatment to be followed, local and general in digestive insufficiency, as met with in various dyspepsias. This book should answer a purpose i.e. to convey practical knowledge to the practitioner; and if at times there seems to be no effort to develop one principal idea, it appears clearly that in all these contributions are to be found the dominating and inspiring teaching of their chief, who for many years has been a prolific writer, an indefatigable clinician, an investigator of note and who has always called for the full cooperation of the laboratory at the bedside.

A. Cantero.

Abstracts

MINOT, GEORGE R.

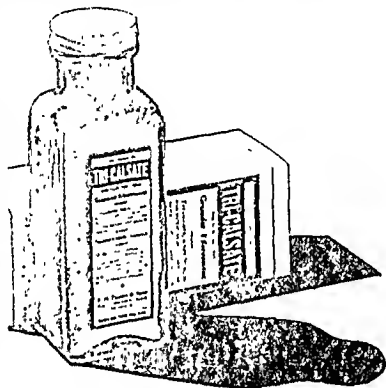
Nutritional Deficiency. Ann. Int. Med., Vol. 12, No. 4, pp. 429-442, Oct., 1938.

The modern concept of deficiency disease is given as the failure of consumption or lack of utilization or loss from the body of vitamins, minerals and other nutritional factors essential for health.

The author then discusses the effect of the utilization of energy on the essential nutritional factors and concludes that, in general, the greater the expenditure of energy the more rapid is the depletion of the nutritional factors responsible for deficiency disease.

The following observations substantiate this view: The more rapid development of scurvy and beriberi in individuals engaged in laborious occupations than in those of sedentary habits, other things being equal; the easy development of deficiency disease during infancy and childhood, and during pregnancy and puerperium, when the demand for the essential factors is greatest; the facility of appearance of deficiency syndromes in thyrotoxicosis because of the greatly increased metabolism.

That exhaustion of the supply of nutritional factors in the body is the essential basis of deficiency disease is also shown by the chronic alcoholic who, although deriving many calories



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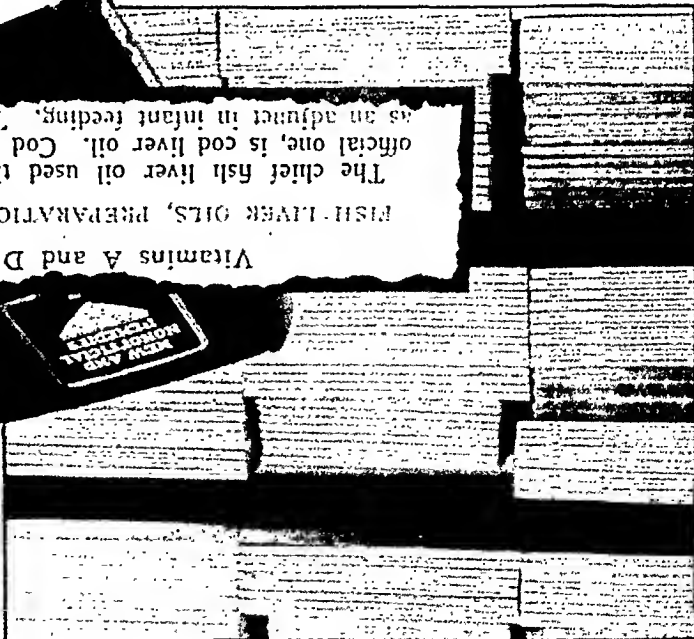
Most of the published work on the vitamins A and D has been based upon the clinical use of cod liver oil. Thus, the vitamins of cod liver oil come to the physician with an imposing array of credentials—published evidence of efficacy.

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from distilled spirits, develops a deficiency syndrome because he chooses a diet lacking or insufficient in the essential nutritional factors.

Gastro-intestinal tract disorders such as improper reduction of raw materials for absorption, alterations in motor and secretory function, the composition of the intestinal contents, gastro-intestinal diseases, and the influence of effects arising outside the gastro-intestinal tract are considered in the development of deficiency disease.

Defective intermediary metabolism of, and inhibitory influences on the

essential nutritional factors result in deficiency diseases.

Loss from the body of the nutritional essentials such as occur in pregnancy, in kidney disease, in effusions, in serous cavities, in suppuration and drainage of wounds, in hemorrhage, lead to deficiency diseases.

The diagnosis, treatment and prevention of nutritional deficiency diseases is the final topic of discussion before the philosophical concluding remarks.

The reviewers consider this paper

a masterful presentation of the subject which should be read in toto.

B. B. Vincent Lyon and
John De Carlo, Philadelphia.

JANKELSON, I. R. AND MCCLURE,
CHARLES W.

Observations on the Clinical Status of Gastroscopy. Vol. 219, No. 23, p. 917, 1938.

With a brief, but complete, introduction to the problem of flexible gastroscopy the authors present ten cases in which the value of this new diagnostic procedure is carefully evaluated and shown to be worth while. The demonstration of posterior wall ulcers, ulcers where the X-ray findings were negative, gastrojejunal ulcers, gastric polyps, cases of hemorrhagic gastritis which were mistaken for bleeding ulcers, gastritis itself, as well as the differential diagnosis between ulcer and carcinoma are some of the examples shown.

They make no extravagant claims for the procedure, but merely advance it as a pertinent and valuable adjunct to diagnostic medicine.

The differential diagnosis between cancer and ulcer, which is so difficult even when the specimen is in the hands of the pathologist or surgeon, they admit cannot be made absolutely by the gastroscopist on a single examination.

The authors mentioned two cases in which they made a gastroscopic diagnosis of carcinoma of the stomach and such a lesion was not found at the operation. They also admitted that other errors of observation or interpretation can occur.

Recently, the adoption of the procedure has become more widespread and in the near future will probably be ranked as an office measure. Unfortunately, however, there has to date been no adequate attempt to control the gastroscopic observations by surgical or autopsy material. This is a step that must precede the establishment of the procedure on a sound basis. The ideal combination would be a gastroscope with a flexible biopsy attachment so that specimens of the gastric mucosa could be taken under direct visualization.

H. H. Lerner.

SUAREZ, RAMON W. AND SAN JUAN,
P. R.

Clinical and Hematological Review of Sprue Based on the Study of 150 Cases. Ann. Int. Med., Vol. 12, No. 4, pp. 529-535, Oct., 1938.

The author presents a review of 150 cases of sprue. Only 2 cases were not natives of Puerto Rico. Whites numbered 121, mulattoes 26 and negroes 3. Ages ranged from 9 to 84 years, one-third of whom were below 40 years.

LAROSTIDIN TREATMENT OF PEPTIC ULCER

*Simple • Easy to Administer •
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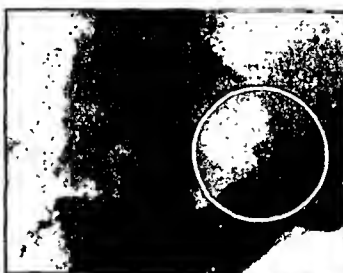
Following are significant excerpts from the conclusions of Mitchell M. Benedict, B.S., M.D., as given in his paper

"Peptic Ulcer and the Larostidin Treatment: A Report on Its Use in One Hundred and Thirty-Two Cases," which

appeared in *The Military Surgeon*, November, 1938: "The parenteral administration of histidine monohydrochloride in 132 cases of gastro-intestinal disorders, 112 of which were peptic ulcer, was followed by rapid remission of clinical symptoms and radiologic evidence of improvement... Regulation of the diet and the mode of living need not be as strict as with other types of treatment... The prompt improvement with the histidine treatment permits the patient to become ambulant early in the treatment... Patients with peptic ulcer tolerate a liberal diet, in the histidine treatment, even during the crisis... The incidence of recurrence was reduced in cases of peptic ulcer receiving the histidine treatment, and all recurrent cases responded satisfactorily to a second treatment... The daily parenteral administration of histidine monohydrochloride has been found the therapy of choice in gastro-intestinal ulcers."



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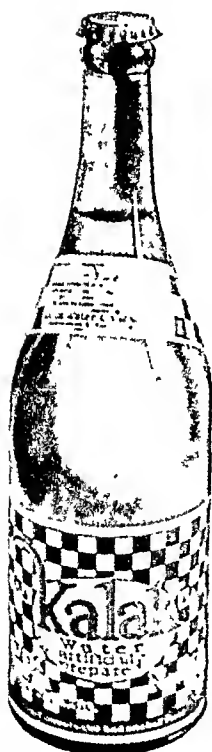
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*In an intensive investigation of respiratory infections, the authors (Pickett-Thomson, Ann. P-T. Res. Lab., p. 605, Dec., '32) found that "There is a decrease in the bicarbonates or reserve bases contained in the blood plasma and the tissues, notably in that of the sodium and calcium salts . . . a lessening of the 'buffer' action of the blood plasma through a decrease in its bicarbonate content."

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The author believes that an hereditary factor is present in the etiology of sprue since in 75% of the cases in which a reliable history could be obtained, sprue or pernicious anemia had existed in one of the parents, usually the mother.

The only concept tenable so far, among the many theories advanced, is that of a deficiency disease. The Puerto Rican diet is inadequate in Vitamin A, probably deficient in B, low in calcium and phosphorus, low in fats, high in carbohydrates, the proteins sufficient in quantity but poor in quality, iron content high. The Puerto Rican diet is compared in all these respects with the continental

diet. The author states that diet alone does not explain the whole story.

In this series the blood pressure was low as a rule, almost universal hypochlorhydria or achlorhydria was found, low fasting blood sugar, flat glucose curves (except when glucose was given intravenously), and low metabolic rates (the last studied in only 10 cases). Tetany was never observed.

The most constant laboratory finding is a macrocytic anemia usually hyperchromic, occasionally hypochromic, never microcytic. A megaloblastic type of marrow was found.

The pancreas was normal in 18 of

the 20 cases autopsied. No osteoporosis or osteomalacia was found.

The disease is regarded primarily as one of the hemopoietic system and not of the gastro-intestinal tract.

The disease responded very well to treatment with concentrated liver extract despite its low Vitamin B content.

The yearly death rate from sprue in Puerto Rico is 65 per million inhabitants.

B. B. Vincent Lyon and
John De Carlo, Philadelphia.

WRIGHT, IRVIN S.

Cevitamic Acid (Ascorbic Acid; Crystalline Vitamin C); a Critical Analysis of its Use in Clinical Medicine. Ann. Int. Med., Vol. 12, No. 4, pp. 516-528, Oct., 1938.

The author presents a method of approach for the determination of the degree of saturation or deficiency of Vitamin C in the body for clinical appraisal.

Three tests are suggested: First, a single determination of cevitamic acid in blood plasma, using the macro method of Farmer and Abt. Second, urinary saturation test which consists in the intravenous administration of 1000 mg. of cevitamic acid and analyzing the urinary excretion of cevitamic acid for the following 5 hours, because the author and his co-workers found that 80% of the 24 hour excretion occurred in the first 5 hours. With kidney disease and nitrogenous retention, the author suggests parallel and blood and urinary determinations to clarify the picture. Third, the capillary fragility test, for which the author suggests the use of the blood pressure apparatus. The sources of errors and fallacies for all of these tests are given.

The symptomatology of scurvy is given and the author stresses the prevalence of the disorder in its pre-clinical forms, in all economic classes.

The curative and maintaining oral dose of cevitamic acid is given as from 30 to 50 mg. per day, but varies greatly in different individuals. Intravenous administration should be used when high oral dosage fails. Large doses of lemon and other citrus fruits have cured cases resistant to cevitamic acid even when given intravenously.

Diseases, other than scurvy, benefited by the administration of cevitamic acid are mentioned.

B. B. Vincent Lyon and
John De Carlo, Philadelphia.

ROBERTSON, ELIZABETH C.

Low Mineral Diets and Intestinal Stasis. University of Toronto Studies. Pathological Series No. 9, 76 pp., 1938.

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hypotonic condition of the colon and consequent constipation. To study this phenomenon, diets which were low in K and Ca were fed to test groups of rats; control groups, consisting of litter mates, were kept on adequate diets. As indicators of stasis, carmine and BaSO₄ both were employed. For the experimental groups, the average excretion times for these substances were 13 and 10 days respectively; for the control groups they were 5 and 4 days respectively. Subsequent feeding of an adequate diet relieved the stasis in all cases. Ca-low diets gave more marked effects than K-low diets; in fact the

effect of K is manifest only when the total mineral intake is kept low. None of these constipational effects were prevented by the presence of roughage (powdered filter paper) or by an increase in the dietary intake of the Vitamin B complex. Such low mineral diets induce a condition of antonomic imbalance.

Similar studies were carried out on a group of 19 hospitalized children. The diets were entirely adequate except with respect to Ca and K. Of these 19 children, 74% became constipated while on the diet. When given a Ba meal, 33% of them retained the Ba in the appendix for as long as

4-21 days. On normal hospital diets, or when the previous diets were supplemented with KCl and Ca-lactate, Ba retention in the appendix never persisted for longer than 24 hours.

Franklin Hollander, New York.

HUBENY, MAXIMILIAN J. AND POLLACK, SIMON.

Diverticulosis of the Small Intestine. Am. J. of Roent. and Rad. Ther., Vol. 40, No. 5, p. 639, 1938.

The authors report an interesting case of diverticulosis of the small intestine, the rarity of which is obvious when we find but thirty cases reported in the literature since 1934. Of these, eight were incidental findings at post-mortem examination.

The theory of locus minoris resistentiae as the etiology is probably the best accepted of all those advanced. The two important factors are the presence of a weak site in the bowel wall at a vascular perforation plus a pulsion force as a result of spasm. The pathology consists of small, multiple, thin walled sacs along the mesenteric border, usually in the upper jejunum. Most cases are multiple and the diverticula themselves may become bifid.

The complaints which may bring the patient to the physician for medical aid are inflammation, hemorrhage, perforation, intestinal obstruction, enterolith formation, and torsion. The symptom complex varies from vague epigastric distress after meals with fullness and eructations, to the clinical picture of peritonitis or obstruction. The diagnosis can only be made by X-ray which shows small round barium filled shadows in films of the small bowel.

H. H. Lerner.

BROWN, WILLIAM REDMAN, HANSEN, ARILD EDSTERN, BURR, GEORGE OSWALD AND MCQUARRIE, IRVINE.

"The Effects of Prolonged Use of Extremely Low-Fat Diet on an Adult Human Subject." Jour. of Nutrition, Vol. 16, p. 511, 1933.

Brown, Hansen, Burr and McQuarrie report an interesting experiment carried out to determine whether the prolonged use of a low-fat diet would exert a harmful affect upon normal human subjects. This experiment was inspired by the results obtained on rats when the young animals placed on a diet low in fat showed retardation or cessation of growth, severe dandruff, scaliness of the feet and tail, hematuria, and premature death. One of the authors acted as subject and lived for some months on a diet limited to sucrose, potato starch, baking powder, sodium chloride, ferric citrate, viosterol, carotene, orange juice, citric acid, anise oil, liquid

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contains **COMPLETE NATURAL
Vitamin B Complex**

... plus All Enzymes, known and unknown factors of **BREWERS YEAST** (no live cells).

(*) Proven Therapy in Gastro-Intestinal Dysfunction. Drs. Dougherty, et al. Jour. Dig. Dis., June, 1938.
Relation of Vitamins to Enzymes. J. A. M. A., July 2, 1938.



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petrolatum and milk freed of its fat. As a result of this diet carried out for six months, no harmful symptoms developed. A slight degree of hypertension disappeared and migraine disappeared. The respiratory quotient rose to more than unity after meals. The iodine number of the total fatty acids of the serum fell from 123 to 93. Also the linoleic acid of the serum was reduced. It cannot be assumed that the human subject could live indefinitely on such a diet devoid of the unsaturated fatty acids.

Howard F. Root, Boston.

CRAFT, CHARLES C.

The Effect of Ephedrine on Pancreatic Secretion; a Method of Management of Patients Having a Pancreatic Fistula. Surgery, 4, 64-73, 1938.

In all, six dogs were provided with complete pancreatoduodenal fistulae; subsequently, these animals were given subcutaneous injections of 10 mg. of ephedrine every two hours. Of nine such experiments, eight yielded decided diminutions in volume of pancreatic juice secreted. Inhibition of secretion reached its maximum during the first hour following injection and had usually disappeared by the end of the second hour. Since there were no toxic manifestations, it is suggested that similar injections of ephedrine may prove helpful in the management of clinical cases of pancreatic fistula. By reducing the flow of pancreatic juice, it may become possible to minimize or prevent erosion by this secretion of the outer abdominal wall surrounding the stoma of the fistula. Another possible method of preventing such erosion is by the use of a dressing made of dry silica gel, which was found effective in treating dogs with leaking fistulae.

Franklin Hollander, New York.

KOMAROV, S. A.

Gastrin. Proc. Soc. Exper. Biol. Med., Vol. 38, p. 514, 1938.

From the pyloric mucosa, and to a lesser degree from the duodenal mucosa, there was extracted a protein-like substance which had a specific secretagogue effect on the fundic gastric glands and which was histamine-free. Pyloric preparations (injected in amounts equivalent to 5 gm. mucosa) elicited a copious secretion of gastric juice of high acidity and low peptic power; this secretion was not abolished by atropine. Fundic and jejunal mucosa preparations elicited a pancreatic but not a gastric secretion. Duodenal preparations elicited a pancreatic secretion and increased bile flow; some gastric se-



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cretion was also evoked. The active principle of pyloric extract is soluble in 80% methyl and ethyl alcohols and dilute acetone, and is precipitated from aqueous solutions by 10 to 30% NaCl, depending on the pH.

M. H. F. Friedman, Detroit.

MYERS, G. NORMAN AND DAVIDSON, S. WHATELY.

An Investigation of the Effects of Certain Substitutes for Morphine and Heroine Upon the Passage of Food Along the Alimentary Tract of the Human Subject. Jour. Hygiene, 38, 432-45, 1938.

The effects on human subjects of a number of drugs—dilaudid, diordid, eukodol—were compared with those of morphine and heroine. Dilaudid and eukodol are very similar to morphine in their effects; tonus of both pyloric and ileocecal sphincters was increased, as a result of which there was a marked delay in passage of food from the stomach into the duodenum and from the small intestine into the cecum. Diordid, however, exerted a much weaker action than morphine or heroine in regard to these sphincters.

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CHASNOFF, JULIUS AND SOLOMON, SYDNEY.

The Takata-Ara Reaction. II. Mechanism—With Special Reference to the Influence of the Ammonia Blood Level. The Jour. of Laboratory and Clinical Medicine, Vol. 23, No. 9, 894-903, June, 1938.

The authors studied the relation between the ammonia content of the blood serum and the Takata-Ara reaction. They found that there was a definite relation between these 2 tests. It was, however, obvious that most cases with a positive Takata-Ara reaction had an alternation of the albumin-globulin ratio. Chasnoff and Solomon believe that the altered albumin-globulin ratio, although not the sole factor, is probably the most important one in the mechanism of the Takata-Ara reaction.

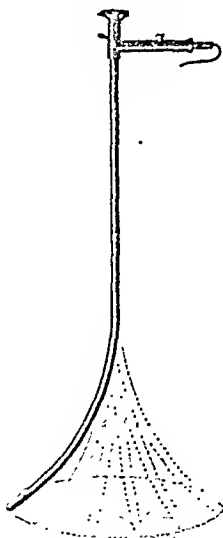
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MARSHALL, WILLIAM A.

Pancreatic Lithiasis, with a Case Report and Autopsy Findings. Radiology, Vol. 31, No. 5, p. 562-566, Nov., 1938.

A case of pancreatic lithiasis is described. Very good roentgenograms show the site of the concretions. The author emphasizes the fact that a plain radiogram of the abdomen is important to arrive at a diagnosis. The routine gastro-intestinal study, with the use of barium, may hide the stones. Early diagnosis is of extreme importance as timely surgery may cure the patient by preventing atrophy and destruction of the glandular tissue. The reported case was complicated by a carcinoma of the body of the pancreas.

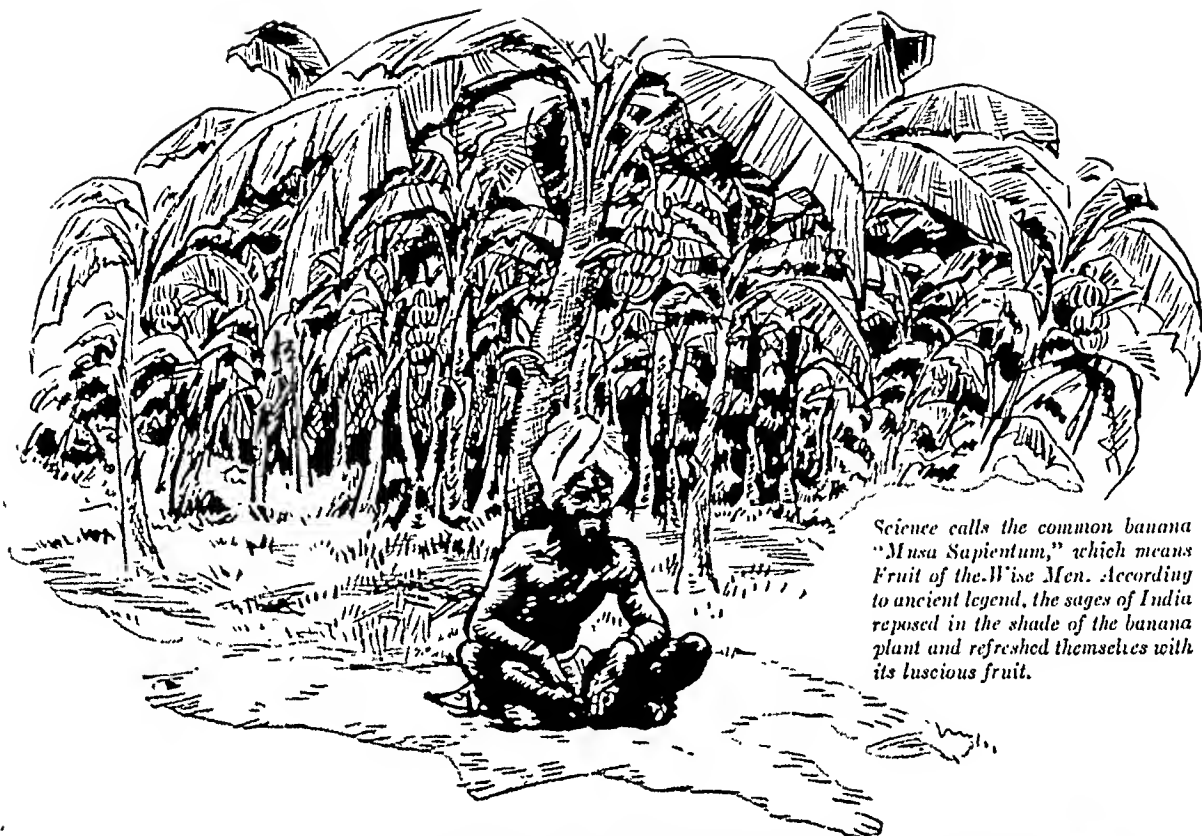
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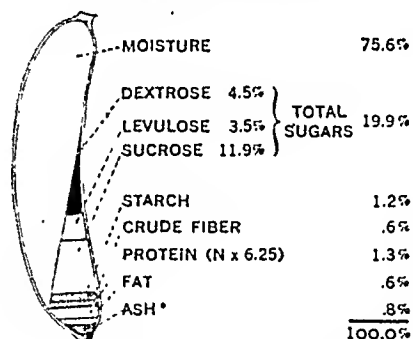
INTERESTING BANANA FACTS

THE ripe banana contains about 20% sugars with nearly 5% other solids consisting of protein, fat, pectins, minerals, vitamins and small amounts of starch and fiber. Its semi-solid texture must hence be attributed to the way in which moisture, sugars and the other constituents are held in a delicate meshwork of cellulose and pectin substances, and *not* to low moisture or high fat content. The sugars present are sucrose, levulose and dextrose. The two simple sugars account for about 40% of the total sugars.

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Readily assimilated sugars (along with vitamins, minerals and fiber)....	.. Infant Feeding
Caloric value (along with vitamins and minerals)....	.. Malnutrition
Satiety value and low fat (along with vitamins and minerals) Reducing Diets
Alkaline residue Combating Acidity
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